DISSERTATION ON

A CASE-CONTROL STUDY OF PREVALENCE AND TYPE OF DYSLIPIDEMIA IN CHRONIC KIDNEY DISEASE

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INTRODUCTION

Chronic Kidney Disease is defined as 'kidney damage with or without decreased GFR, manifested as either pathological abnormalities or presence of markers of kidney damage, including abnormalities in composition of blood or urine, abnormality renal imaging findings, for at least 3 months, or by a GFR below 60 ml/min/1.73 m^2 body surface area'[1]. This broad definition includes patients with or without symptoms of kidney disease.

CARDIOVASCULAR DISEASE IN CKD:

CKD is a worldwide health problem. According to World Health Organization Global Burden of Disease project, CKD is the 12 th leading cause of death and 17th cause of disability[2]. The incidence of ESRD is increasing worldwide at an annual growth rate of 8%[3].

ESRD patients have extremely high morbidity and mortality from CVD. Based on data from the U.S. Renal Data System Coordinating Centre - Case Mix Adequacy Study, the prevalence of clinical coronary heart disease in hemodialysis patients is 40%, and CVD mortality is 10 to 30 times higher than in the general population despite stratification by gender, age, race, and the presence of diabetes[4].

The exact prevalence of CKD in India is not clear and the quality of that provided by small observational studies & personal experiences is quiet uneven. A small beginning has been made by the start of CKD registry in India

(www.ckdri.org). There are only three population based studies in India. In a prevention program started at community level in Chennai, the reported prevalence is 0.86% in the project population and 1.39% in the control region. The second study is based on Delhi involving 4972 urban patients. The prevalence of CKD (defined as serum creatinine more than 1.8 mg/dl) was 0.79 % or 7852 per million/population. The third study, perhaps the only longitudinal study to identify the incidence of ESRD is based on 572,029 subjects residing in city of Bhopal suggests that the average crude and age adjusted incidence rates of ESRD were 151 and 232 per million population respectively[5]. **"Screening and Early Evaluation of Kidney Disease" (SEEK) study** was started in 2006 in India which has reported a very high prevalence of 17.4% of CKD among 5,623 participants; 7% out of these were in CKD Stage 1; 4.3% were in CKD Stage 2; 5% were in CKD Stage 3 and 1.6% in CKD Stage 4 and 5.

India is projected to become the major reservoir of chronic diseases like diabetes and hypertension. Since 25–40% of these subjects may develop CKD, the ESRD burden will rise. In absolute numbers the countries with the largest projected number of cases in 2030 will be India (79.4 million), China (42.3 million) and the USA (30.3 million)[6].

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients at every stage of CKD. The incremental risk of CVD in those with CKD compared to the general population ranges from 10 to 200 fold, depending on the stage of CKD. 30-45% of patients reaching stage 5 CKD

already have advanced cardiovascular complications. As a result, most patients with CKD succumb to cardiovascular disease before ever reaching stage 5 CKD. Thus, the focus of patient care in earlier CKD stages should be directed to the prevention of cardiovascular complications[7].

The increased prevalence of vascular diseases in CKD patients derives from both traditional ("classic") and non-traditional (CKD-related) risk factors. Traditional risk factors include hypertension, hypervolemia, **dyslipidemia**, sympathetic over activity and hyperhomocysteinemia. Non Traditional Risk Factors are proteinuria, homocysteinemia, lipoprotein(a) and apolipoprotein(a) isoforms abnormality, anemia, abnormal calcium / phosphate metabolism, extracellular fluid overload, oxidative stress, inflammation, malnutrition and thrombogenic factors.

DYSLIPIDEMIA IN CKD:

The most common dyslipidemia observed in patients with CKD is atherogenic dyslipidemia—a combination of hypertriglyceridemia and low levels of high-density lipoprotein cholesterol[8]. Dyslipidemia is believed to play a role in both the development of cardiovascular disease and the progression of renal disease regardless of the underlying cause (e.g., diabetes, hypertension) [9,10]. Increased levels of lipoprotein (a) are also common in CKD[11].

Consequently, detecting & treating dyslipidemia in this population is as important as in populations without renal disorders, in order to prevent the development of CVD.

The principal reason of this study is to find out the prevalence of dyslipidemia in CKD patients either on conservative therapy or dialysis, irrespective of aetiology except Diabetes Mellitus & Nephrotic syndrome (since they are independent risk factors for dyslipidemia) & to find out the type of hyperlipidemia in these patients and to compare it with the age & sex matched controls.

AIMS AND OBJECTIVES

a) To study the prevalence of dyslipidemia in chronic kidney disease, excluding diabetic and nephrotic aetiology and to compare it with the control population.
b) To examine which type of hyperlipidemia predominates in these patients.
c) To study whether any correlation exist between severity of CKD and lipid alteration.
d) To study whether there is any difference in the pattern of dyslipidemia between CKD patients on conservative treatment and those on hemodialysis.

MATERIALS AND METHODS

STUDY POPULATION:

Hospital based 80 CKD patients in Chengalpattu Government Hospital (out-patient & in-patient) from September 1st, 2009 to November 30th, 2010.

CONTROL POPULATION:

Age & sex matched 80 normal healthy controls are selected from the same hospital, who came with different illness other than the study disease.

SELECTION CRITERIA FOR CASES:

a. CKD patients on conservative therapy (at diagnosis) or dialysis (three months after initiating dialysis), irrespective of aetiology except nephrotic proteinuria and diabetes mellitus.
b. Patients with serum creatinine ≥ 2 mg/dl AND bilateral contracted kidneys.
    - Patients are selected if they have bilateral contracted kidneys in ultrasonography of the abdomen i.e., if the kidneys in long axis are less than 9 cm and a serum creatinine ≥ 2 mg/dl.

EXCLUSION CRITERIA FOR BOTH CASES AND CONTROLS:

Exclude patients who are obese, with diabetes mellitus, those on beta - blockers & oral contraceptive pills, pregnant patients, patients with history of smoking and chronic alcohol intake.

Diabetes mellitus is ruled out by fasting and post-prandial blood sugar. Patients are excluded if they have FBS ≥ 100mg/dl & PPBS ≥140 mg/dl.

Protein-to-creatinine ratio in early morning urine sample is used to exclude nephrotic proteinuria. Urine protein in mg and urine creatinine in mg is noted & their ratio is calculated. Cases were excluded if the ratio was >3.5 (correlates with 3.5 gm protein/24 hrs urine sample)[12]. There is a high degree of correlation between 24-hour urine protein excretion and protein-to-creatinine ratios in random, single-voided urine samples[12].

Obese patients are excluded since they have high VLDL & reduced HDL[13]. Obesity classification was based on Body Mass Index (BMI) which takes into account the weight and height of the patient. BMI = wt in kg / ht in m^2. If BMI was ≥ 25 kg/m^2, patients were excluded.

Pregnant patients were excluded since VLDL is elevated in pregnancy[13].

Those on OCPs were excluded, since the oestrogen component increases HDL[13].

Beta blockers elevate VLDL & reduce HDL[13], hence patients consuming it were excluded.

A subject was classified as a non-smoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime and had stopped smoking at least 1 year back[14]. A non-drinker was classified as one who had never consumed alcoholic beverages[14]. Alcohol elevates HDL & VLDL, while smoking reduces HDL[13], hence they were excluded.

In the proforma, detailed history regarding the presenting symptoms like fatigue, weakness, pruritis, anorexia, nausea, vomiting, nocturia, polyuria, oliguria, insomnia, oedema, difficulty in breathing, etc., was enquired. Past history & history of dialysis was obtained. General examination including pallor, pulse rate, blood pressure, height & weight were noted & BMI calculated. Cardiovascular system, respiratory system, per abdomen examination & central nervous system examination including fundus examination was done.

The following laboratory investigations were obtained – haemoglobin (g/dl), blood sugar – fasting & post prandial (mg/dl), blood urea (mg/dl), serum creatinine (mg/dl), electrolytes – sodium, potassium, chloride & bicarbonate (mEq/L). Creatinine clearance was calculated. Ultrasonography of the abdomen was done to measure the kidney size. Fasting lipid profile was done – Total Cholesterol (TC), Triglycerides (TG) and High Density Lipoproteins (HDL) were measured and Low Density Lipoproteins (LDL), Very Low Density Lipoproteins (VLDL) & TC/HDL ratio were calculated. Electrocardiogram, urine analysis & spot urine protein creatinine ratio were also done. All the data collected were analysed using SPSS (Statistical Package for the Social Science) system.

METHODOLOGY OF INVESTIGATIONS:

TOTAL CHOLESTEROL:

Method – Enzymatic one step method of Wybenga & Pileggi.

Principle – Cholesterol reacts with hot solution of Ferric perchlorate, Ethyl acetate & sulphuric acid (cholesterol reagent) and gives a lavender coloured complex which is measured at 560 nm.

Cholesterol esters ---$^{\text{cholesterol esterase}}$----> Cholesterol + Fatty acid

Cholesterol +O_2 ---------- > Choleston-3-one + H_2O_2

2 H_2O_2 + Phenolic compound --------- > Quinonenine

Sample – serum / plasma (after a 12 hr overnight fast).

Reagents – Reagent 1: Cholesterol reagent

Reagent 2: Working cholesterol standard 200%

Reagent 3: Precipitating reagent

Procedure:

Mark 3 test tubes as Blank (B), Standard (S) & Test (T).

	BLANK	**STANDARD**	**TEST**
REAGENT 1	3 ml	3 ml	3 ml
REAGENT 2	-	0.015 ml	-
SERUM / PLASMA	-	-	0.015 ml

Mix well & keep the 3 test tubes in a boiling water bath for 90 seconds. Cool them immediately to room temperature, under running tap water. Measure the Optic Density (OD) of B, S & T on a calorimeter with a yellow-green filter or on a spectrophotometer at 560 nm.

Total cholesterol = (OD Test / OD Standard) x 200

HIGH DENSITY LIPOPROTEIN:

HDL is obtained in the supernatant after centrifugation using the same reagents mentioned above.

Pipette 0.2 ml of the sample & 0.2 ml of the precipitating reagent, mix well, keep at R.T. for 10 min and then centrifuge at 2000 rpm for 15 min to obtain a clear supernatant.

	BLANK	**STANDARD**	**TEST**
REAGENT 1	3 ml	3 ml	3 ml
REAGENT 2	-	0.015 ml	-
SUPERNATANT	-	-	0.12 ml

Mix well & keep the tubes immediately in boiling water bath for 90 sec & cool them immediately to room temperature, under running tap water. Measure the Optic Density (OD) of B, S & T on a calorimeter with a yellow-green filter or on a spectrophotometer at 560 nm.

HDL cholesterol = (OD Test / OD Standard) x 50

TRIGLYCERIDE:

Method: Enzymatic – calorimetric method.

Sample: Fasting samples of serum / EDTA or heparinised plasma.

Principle:

$$\text{Triglycerides} + H_2O_2 \xrightarrow{\text{lipoprotein lipase}} \text{Glycerol} + \text{Fatty acid}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{glycerol kinase, Mg2}} \text{Glycerol-3-phosphate} + \text{ADP}$$

$$\text{Glycerol-3-phosphate} + O_2 \xrightarrow{\text{GPO}} \text{Dihydroxyacetone Phosphate} + H_2O_2$$

$$2H_2O_2 + \text{4-aminoantipyrine} + \text{ADPS} \xrightarrow{\text{peroxidise}} \text{Red Quinone}$$

GPO – Glycerol-3-phosphate Oxidase

ADPS – N-ethyl-N-93-sulfopropyl)-m-anidisin

The intensity of the purple coloured complex formed is directly proportional to the TG concentration in the sample measured at 546 nm.

REAGENT 1 (Enzymes / Chromogen): Lipoprotein lipase, Glycerol kinase, Glycerol-3-phosphate oxidase, peroxidise, 4-aminoantipyrine & ATP.

REAGENT 1A (Buffer): Pipes buffer, ADPS, Magnesium salt.

STANDARD (TG 200 mg/dl): Glycerol.

Method: Mix reagent 1 & 1A and bring it to R.T.

	BLANK	**STANDARD**	**TEST**
RECONSTITUTED REAGENT	1 ml	1 ml	1 ml
STANDARD	-	10 ul	-
SAMPLE	-	-	10 ul

Incubate for 5 min at 37^{o} C. Mix and read at 546 nm.

VLDL-C is calculated using the formula,

VLDL-C = triglycerides / 5

LDL-C is estimated using the following equation:

LDL-C = total cholesterol – (TG/5) – HDL-C

The **National Cholesterol Program (NCEP) Adult Treatment Panel (ATP) III guidelines** indicate that the upper limit of normal for total cholesterol is 240 mg/dl, LDL- C is 130 mg/dl, TG is 200 mg/dl and the lower limit for HDL- C is 35 mg/dl. Hence study and control population with values crossing the above mentioned limits were considered to have dyslipidemia.

BLOOD UREA:

Urea was one of the first indicators used to measure GFR. Urea production is variable and is largely dependent on protein intake. With a molecular weight of 60 Daltons, urea is freely filtered at the glomerulus, but readily reabsorbed in the tubules, and the amount of tubular reabsorption is variable, because of which renal urea clearance usually underestimates the GFR.

Increased plasma urea levels are seen in decreased urine flow as occurring in patients with intravascular volume depletion, following diuretic intake[15] and congestive heart failure. Increased urea due to increased production is seen with elevated dietary protein intake[16], gastrointestinal bleeding, and tetracycline use.

On the other hand, reduced levels of plasma urea can be seen in patients with alcohol abuse and chronic liver disease[17].

Method: Mix 4 ml of buffer reagent with 1 ml of enzyme reagent.

	STD	SAMPLE
SAMPLE	-	10 ul
STANDARD	10 ul	-
REAGENT	1000 ul	1000 ul

Mix well & read after 30 secs initial absorbance of sample (A1s) and standard (A1std) and start timer simultaneously. Read again after 60 secs (A2s & A2std) at 340 nm.

Calculation and linearity:

UREA (mg/dl)= (A2s –A1s) / (A2std – A1std) X 50

SERUM CREATININE:

Creatinine is small (molecular weight 113 Daltons), does not bind to plasma proteins, freely filtered by the renal glomerulus & also secreted by the renal tubule. Creatinine production is proportional to muscle mass. Age- and gender-associated differences are also largely attributable to differences in muscle mass.

A number of methods are used to measure creatinine[18,19].

a) The original **Folin-Wu method** used the **Jaffe's reaction**, which is being used with various modifications. The Jaffe's reaction has also been adapted for use in auto analyzers.

METHOD: Creatinine reacts with alkaline picrate in the reagent & form reddish-orange complex, known as creatinine picrate which is measured calorimetrically.

REAGENT: 0.75N NaOH, 0.04 N Picric acid, creatinine standards of various concentrations.

PROCEDURE: Add 250 uL of picric acid with 250 uL of Sodium hydroxide in a test tube to which 50 uL of blood is added at room temperature. Reading is taken at 515 nm in the calorimeter.

b) The **method of Hare,** involved the isolation of creatinine by absorption on **Lloyd's reagent**[20].

c) The **direct alkaline picrate method of Bonsnes and Taussky**[18].

d) Other methods currently in use employ O-nitrobenzaldehyde (**Sakaguchi reaction**) and imidohydrolase[19].

Glucose, fructose, pyruvate, acetoacetate, uric acid, ascorbic acid, cephalosporin and plasma proteins can all cause the Jaffe's colorimetric assay to yield falsely high creatinine values[21]. Auto analyzer methods utilize the Jaffe's reaction, but separate creatinine from non-creatinine chromogens by the rate of colour development[22], thus avoiding most of the interference seen with the standard Jaffe's method[23]. However, very high serum bilirubin levels can cause falsely low creatinine.

Serum creatinine is probably the most widely used indirect measure of GFR, its popularity being attributed to convenience and low cost. Unfortunately, it is very insensitive to even substantial decline in GFR. The GFR (measured by more accurate techniques described later) may be reduced by up to 50% before serum creatinine becomes elevated.

GLOMERULAR FILTRATION RATE (GFR):

GFR is traditionally measured as the renal clearance of a particular substance or marker from plasma. The clearance of an indicator substance is the amount removed from plasma, divided by the average plasma concentration over the time of measurement, expressed in moles or weight of the indicator per volume per time.

Indeed, if we assume that there is no extra-renal elimination, tubular reabsorption or tubular secretion of the marker, then GFR can be calculated as follows:

$$\textbf{Glomerular filtration rate} = (U \cdot V) / (P \cdot T)$$

where U is the urine concentration, V is the urine volume, and P is the average plasma concentration of the marker over the time (T) of the urine collection.

Characteristics of an ideal endogenous or exogenous marker for measuring GFR - constant production, safe, convenient, readily diffusible in extracellular space, no protein binding, freely filterable, no tubular reabsorption, no tubular secretion, no extra renal elimination or degradation, accurate &

reproducible assay, no compound should interfere, inexpensive and no influence on the GFR.

Estimated - GLOMERULAR FILTRATION RATE (e-GFR):

GFR can be calculated using the below formulae

1) Cockcroft and Gault formula:

e-GFR (ml/min)= [(140-age in yrs) x weight in kg] / (72 x s. creatinine)

multiply by 0.85 if female[24]

2) Equation from the Modification of Diet in Renal Disease study (MDRD):

e-GFR (ml/min/1.73 m^2) = 1.86 x (Plasma creatinine) – 1.154 x (age) – 0.203

Multiply by 0.742 for women

Multiply by 1.21 for African Americans

Other formulae for e-GFR using serum creatinine and other clinical parameters:

Formula	**Units**	**Reference**
(100/Cr) - 12 if male	ml/min/1.73 m^2	Jelliffe[25]
(80/Cr) - 7 if female		
(Wt · (29.3 - 0.203 · Age)/(Cr · 14.4), if male	ml/min	Mawer[26]
(Wt · (25.3 - 0.175 · Age)/(Cr · 14.4), if female		
(98 - 16 · (Age - 20)/20)/Cr, multiply by 0.90 if female	ml/min/1.73 m^2	Jelliffe[25]
((145 - Age)/Cr) - 3, multiply by 0.85 if female	ml/min/70 kg	Hull[27]
(27 - (0.173 · Age))/Cr, if male	ml/min	Bjornsson[28]
(27 - (0.175 · Age))/Cr, if female		
7.58/(Cr · 0.0884) - 0.103 · Age + 0.096 · Wt - 6.66,	ml/min/1.73 m^2	Walser[29]

Formula	Units	Reference
if male		
6.05/(Cr · 0.0884) - 0.080 · Age + 0.080 · Wt - 4.81, if female		
$170 \cdot Cr^{-0.999} \cdot Age^{-0.176} \cdot (0.762$ if female) · (1.180 if black) · $SUN^{-0.170} \cdot Alb^{0.318}$	ml/min/1.73 m^2	Levey[30]

Limitations of e-GFR (where creatinine clearance should be measured):

a) Extremes of age

b) Severe malnutrition / obesity

c) Pregnant women

d) Disorders of skeletal muscle

e) Critically ill, paraplegia, quadriplegia & hospitalised patients since they lack stable renal function

f) Prior to dosing drugs with severe toxicity & narrow therapeutic index.

ULTRASOUND:

Sonographic images of the kidneys are generally obtained in the longitudinal and transverse planes. Overall renal echogenicity is generally compared with the liver on the right and the spleen on the left. The normal renal cortex is less echogenic than the liver and spleen. Underlying liver disease may alter this picture. The medullary pyramids are hypoechoic and their triangular shape points to the renal hilum. The renal cortex lies peripherally and the

separation from the medulla is usually demarcated by an echogenic focus due to the arcuate arteries along the corticomedullary junction.

Renal size is easily measured sonographically. The normal longitudinal dimension of right kidney is 11 ± 1 cm and the left kidney is 11.5 ± 1 cm. The demonstration of increased echogenicity within the renal cortex may be useful in suggesting the presence of renal parenchymal (medical renal) disease[31]. The renal cortex may show increased echogenicity in patients with either acute or chronic kidney injury and this is generally related to interstitial fibrosis. The finding is bilateral. A patient with small, echogenic kidneys usually has ESRD.

REVIEW OF LITERATURE

CHRONIC KIDNEY DISEASE:

Criteria

Kidney damage for ≥3 months, with or without decreased GFR
• Pathological abnormalities
• Markers of kidney damage
  • Urinary abnormalities (e.g., proteinuria)
  • Blood abnormalities
  • Imaging abnormalities
• Kidney tra□splantation

GFR <60 ml/min/1.73 m^2 for ≥3 months, with or without kidney damage

STAGES OF CKD:

The recent Kidney Disease Outcomes Quality Initiative **(K/DOQI 2002) guidelines** have classified CKD into five stages[32]:

Stage	**Description**	**GFR (ml/min/1.73 m^2)**
0	with risk factors for CKD	>90
1	kidney damage[a] with normal or ↑ GFR	≥90
2	kidney damage with mild ↓ GFR	60–89
3	moderate ↓ GFR	30–59
4	severe ↓ GFR	15–29

Stage	Description	GFR (ml/min/1.73 m^2)
5	kidney failure	<15 (or dialysis)

a - kidney damage includes persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry or abnormal imaging.

HISTORICAL ASPECTS:

In 1773 **urea** was first isolated from human urine by **Rouelle**, and in 1800 **Fourcroy** coined the term **"urea"**. The term **uremia** was coined by **Piorry & L'Heritier** in 1840 which means 'retention in blood of urea & other products of metabolism normally excreted in urine'.

Uremia is a complex condition with characteristic features resulting from renal failure, which causes accumulation of unexcreted waste products. Thus not all patients with renal failure are uraemic.

In 1836, **Richard Bright** commented on the "**milky serum**" of patients with ESRD – almost certainly the first recognition of hyperlipidemia.

In 1903, **Strauss** introduced blood urea as a diagnostic test for renal diseases[33] and finally in 1931, **Jolliffe and Smith** introduced the concept of **creatinine clearance** for practical application.

In 1926, **Rehberg** used exogenous creatinine to measure renal clearance as an estimate of GFR. In 1928, the concept of urea clearance as a measure of kidney function was described in detail by **Moller, McIntosh, and Van Slyke**.

Association between lipid abnormalities & renal disease was suggested by **Virchow** in 1860. **Munk** coined the term '**Lipoid nephrosis**'.

RISK FACTORS:

Non-modifiable risk factors:

- Genetic factors
- Racial factors - A large single-centre study in the UK of 771 patients with ESRD, showed a higher incidence of DN in patients from the Indian subcontinent, while hypertensive renal disease was more common in individuals of Caribbean and African descent (Pazianas et al. 1991). This was confirmed by a study in which Indo-Asians were shown to have higher susceptibility to DN (Buck and Feehally 1997). Furthermore, UK Asians with DN may have a faster rate of decline of GFR when compared to Caucasians.
- Gender - ESRD is more common in males[34].
- Age - The K/DOQI review of 21 studies suggested that age was a risk factor for the progression of CKD[34]. One notable exception is type 1 DM where young age at diagnosis is associated with a faster rate of GFR decline.

Modifiable risk factors:

- Hypertension - has been shown to be both an initiation and progression factor for diabetic and other nephropathies.

- Proteinuria - the majority of studies showed an association between heavy proteinuria and a faster rate of GFR decline by univariate analysis.
- Glycaemia - poor blood glucose control is a major factor in the initiation of nephropathy in susceptible diabetics, but evidence for a role in progression is conflicting.
- Lipids - lipids may contribute to the initiation and progression of CKD as data from the **Atherosclerosis Risk in Communities (ARIC) study** in the United States has shown that hyperlipidemia (especially triglyceridaemia) is associated with an increased risk of ESRD[35].
- Others - hyperuricaemia, obesity, smoking, caffeine, alcohol and recreational drugs like heroin or opiates.

The role of lipids in progressive kidney scarring - Glomerulosclerosis: Lipid hypothesis focused on the nephrotoxicity of lipids (Moorhead **et al**. 1982). Glomerular toxicity of lipids has included an increase in Pgc as well as functional and structural endothelial and mesangial changes. Glomerular endothelial and mesangial cells have receptors for both LDL and oxidized-LDL. LDL accumulates in the mesangial cells and matrix in dyslipidemic states (Schlondorff 1993). Under conditions of glomerular oxidative stress such as inflammation, deposited LDL undergoes oxidative modifications. This would, in turn, induce further inflammatory changes through the release of Monocyte Chemoattractant Protein-1 (MCP-1). This

would stimulate the influx of monocytes to the glomeruli and exacerbate glomerular injury. Such infiltration often precedes glomerulosclerosis. Reduction of hyperlipidemia by dietary or pharmacological means is protective in models of spontaneous and experimental glomerulosclerosis.

CAUSE OF CHRONIC KIDNEY DISEASE AND END STAGE RENAL FAILURE:

- Arteriopathic, i.e., renovascular disease, hypertensive disease
- Diabetic ESRD
- Glomerulonephritis
- Infective / obstructive (chronic pyelonephritis, reflux nephropathy, benign prostatic hypertrophy, neurogenic bladder, renal stones disease)
- Congenital / familial / hereditary (e.g. adult polycystic kidney disease, Alport's syndrome, cystinosis, oxalosis)
- Toxic, e.g., drug induced such as analgesic nephropathy, other toxic agents
- Neoplasms, e.g., kidney tumours
- Systemic, e.g., myeloma, systemic lupus erythematosus, amyloidosis, henoch schonlein purpura, scleroderma, haemolytic uremic syndrome
- Miscellaneous, e.g., Balkan nephropathy
- Uncertain

PREVALENCE OF CKD:

Prevalence of CKD (GFR ≤ 60 ml/min/1.73 m^2) according to National Health and Nutrition Examination Survey [**NHANES**] in US from 1999–2000 with a study population of 4,101 was 3.8 **%.**

The last 2 decades have witnessed an epidemic growth in the number of subjects with type 2 diabetes, typically in association with obesity and increasing sedentary lifestyle[36]. Given the relatively slow natural history of diabetic glomerulosclerosis, it is possible that we are only beginning to see the impact of this increase in diabetes on the occurrence of kidney injury and that, this is shown as an increase in the prevalence of proteinuria and early stages of CKD as seen in NHANES 1999-2000 relative to the 1988-1994 survey[37]. Thus, there is an ominous possibility that an increased prevalence of diabetes will considerably escalate future rates of CKD.

EVALUATION OF CHRONIC KIDNEY DISEASE:

Stage	Evaluation Plan
0	Screening CKD risk reduction
1	Diagnose and treat cause, slow the progression, evaluate risk of cardiovascular disease
2	Estimate progression
3	Evaluate and treat complications
4	Prepare for renal replacement therapy
5	Initiate renal replacement therapy

CARDIOVASCULAR DISEASE AND CHRONIC KIDNEY DISEASE:

Traditional Risk Factors like older age, male gender, hypertension , high LDL, low HDL, diabetes, smoking, physical inactivity, menopause, family history of CVD & left ventricular hypertrophy and **Non Traditional Risk Factors** like proteinuria, homocysteinemia, lipoprotein(a) and apolipoprotein(a) isoforms abnormality, anemia, abnormal calcium / phosphate metabolism, extracellular fluid overload, oxidative stress, inflammation (C-reactive protein), malnutrition, thrombogenic factors[38] are similar for CKD & CVD.

It is well established that patients with kidney failure are at high risk of cardiovascular mortality[39,40]. Patients with CKD experience a high rate of fatal and nonfatal CVD events prior to reaching ESRD[41,42]. Patients in all stages of CKD are therefore considered in the "*highest risk group*" for development of CVD and CKD is also recognized as a '*cardiovascular risk equivalent*'[43-45].

Cardiovascular mortality, defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease or pulmonary edema in the general population (**NCHS multiple cause of mortality data files ICD** 9 codes 402, 404, 410–414, and 425-429, 1993) was low when compared with CKD group[46].

The relationship between CKD and CVD is complex - CKD is a risk factor for CVD and CVD may be a risk factor for CKD. Several cardiovascular risk factors promote the development and progression of both CKD and CVD.

Declining kidney function, in turn, is associated with elevated levels of cardiovascular risk factors[47].

CARDIOVASCULAR DISEASE RISK FACTORS AS RISK FACTORS FOR CKD:

1) *Hypertension*

2) *Diabetes* - In the **United Kingdom Prospective Diabetes Study (UKPDS)**, 10 years after diagnosis of diabetes, the prevalence of microalbuminuria was 25%, macroalbuminuria 5.3% and elevated plasma creatinine or kidney failure was 0.8%[48]. In the **Framingham Heart Study offspring cohort**, baseline dysglycemia was associated with future risk of developing CKD[49]. Among patients with diabetes, there appears to be a strong relationship between poor metabolic control and the risk for development of diabetic kidney disease.

3) *Smoking* - In cross-sectional analysis of a population sample of 28,409 individuals who were smokers (both former and current smoking), it was found that smoking was associated with an approximately 3 fold increased risk of proteinuria[50]. In a prospective study of patients with CKD, smoking cessation was associated with decreased rate of progression and postponement of kidney failure over a 2-year follow-up[51].

4) ***Dyslipidemia*** - In the **Atherosclerosis Risk In Communities (ARIC) Study**, high TG and low HDL-C were associated with an increased risk of

developing decreased kidney function. The **Cholesterol and Recurrent Events (CARE) Study** - a randomized double-blind placebo controlled trial of Pravastatin versus placebo in participants with previous MI and total plasma cholesterol <240 mg/dl, showed that Pravastatin appeared to slow the rate of loss of kidney function[52].

5) *Metabolic syndrome*

LIPOPROTEIN METABOLISM:

Lipoproteins are large macromolecular complexes that transport hydrophobic lipids (triglycerides [TG], cholesterol, and fat-soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to and from tissues. They play an essential role in the absorption of dietary cholesterol, long chain fatty acids, and fat-soluble vitamins; the transport of TG, cholesterol and fat-soluble vitamins from the liver to peripheral tissues; and the transport of cholesterol from peripheral tissues to the liver.

Lipoproteins contain a core of hydrophobic lipids (TG and CE) surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins that interact with body fluids.

The plasma lipoproteins are divided into 5 major classes based on their relative density: chylomicrons, very low density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs). Most of the plasma TG is transported in

chylomicrons or VLDLs and most plasma cholesterol is carried as CE in LDLs and HDLs.

The proteins associated with lipoproteins, called apolipoproteins, are required for the assembly, structure and function of lipoproteins. They activate enzymes important in lipoprotein metabolism and act as ligands for cell surface receptors. ApoA-I, which is synthesized in the liver and intestine, is found on virtually all HDL particles. ApoA-II is the second most abundant HDL apolipoprotein and is on approximately two-thirds of all HDL particles. ApoB is the major structural protein of chylomicrons, VLDLs, IDLs, and LDLs; one molecule of apoB, either apoB-48 (chylomicron) or apoB-100 (VLDL, IDL or LDL), is present on each lipoprotein particle. The human liver synthesizes apoB-100, and the intestine makes apoB-48 by mRNA editing. ApoE is present in multiple copies on chylomicrons, VLDL, and IDL, and it plays a critical role in the metabolism and clearance of TG-rich particles. ApoC-I, ApoC-II and ApoC-III also participate in the metabolism of TG-rich lipoproteins.

THE EXOGENOUS AND ENDOGENOUS LIPOPROTEIN METABOLIC PATHWAYS:

Transport of Dietary Lipids (Exogenous Pathway):

Dietary TGs are hydrolyzed by lipases within the intestinal lumen and emulsified with bile acids to form micelles. Dietary cholesterol, fatty acids, and fat-soluble vitamins are absorbed in the proximal small intestine. Cholesterol

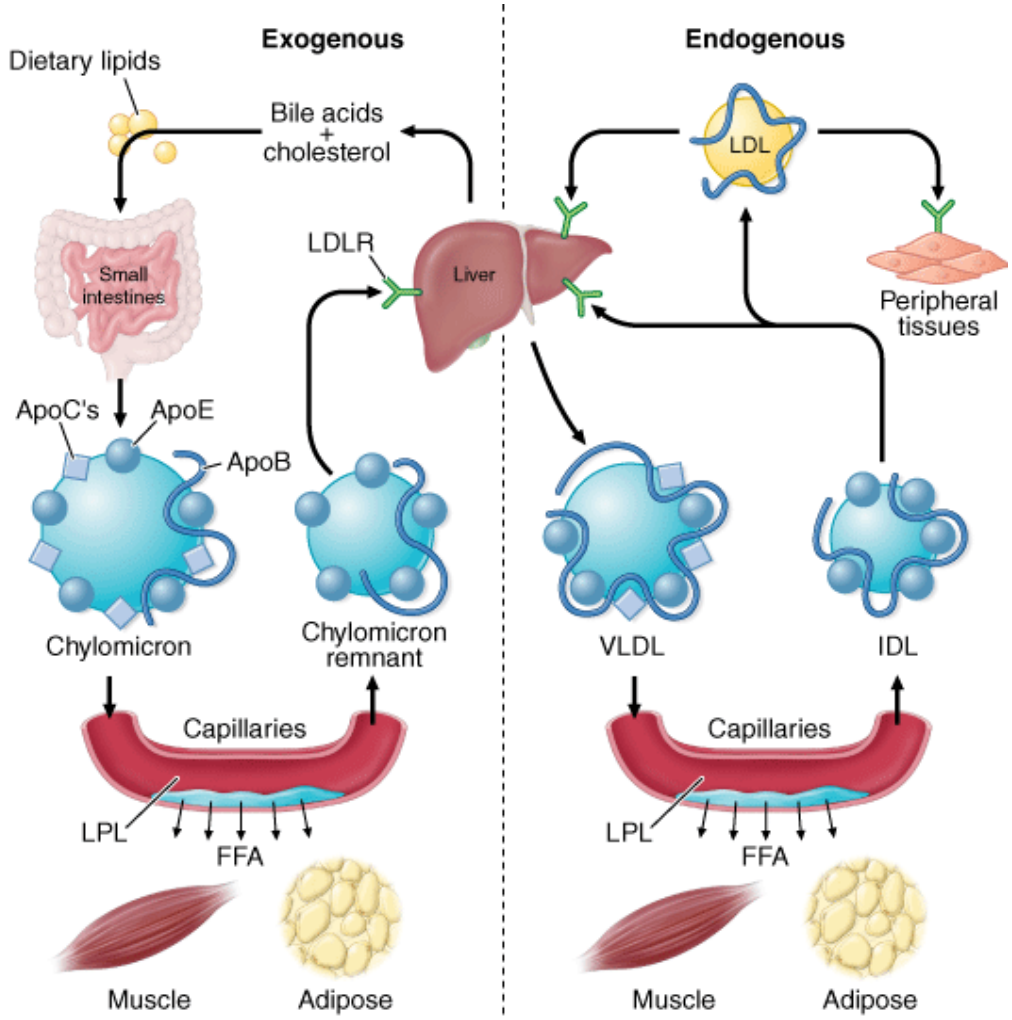
and retinol are esterified in the enterocyte to form CE and retinyl esters, respectively. Longer-chain fatty acids (>12 carbons) are incorporated into TG and packaged with apoB-48, CE, retinyl esters, phospholipids and cholesterol to form chylomicrons. Nascent chylomicrons are secreted into the intestinal lymph and delivered via the thoracic duct directly to the systemic circulation. The particles encounter LPL, which is anchored to proteoglycans in the capillary endothelial surfaces of adipose tissue, heart and skeletal muscle. The TGs of chylomicrons are hydrolyzed by LPL and FFAs are released. ApoC-II, which is transferred to circulating chylomicrons from HDL, acts as a cofactor for LPL in this reaction. The released FFA is taken up by adjacent myocytes or adipocytes and either oxidized to generate energy or reesterified and stored as TG. The chylomicron particle progressively shrinks in size as the hydrophobic core is hydrolyzed and the hydrophilic lipids and apolipoproteins on the particle surface are transferred to HDL, creating chylomicron remnants, which are rapidly removed from the circulation by the liver through a process that requires apoE as a ligand. Consequently, few, if any, chylomicrons or its remnants are present in the blood after a 12-h fast, except in patients with disorders of chylomicron metabolism.

Transport of Hepatic Lipids (Endogenous Pathway):

It refers to the hepatic secretion of apoB-containing lipoproteins and their metabolism. VLDL particles resemble chylomicrons, in protein composition but

contain apoB-100 rather than apoB-48 and have a higher ratio of cholesterol to TG (~1 mg of cholesterol for every 5 mg of TG). The TGs of VLDL are derived predominantly from the esterification of long-chain FA in the liver. The packaging of hepatic TG with the other major components of the nascent VLDL particle (apoB-100, CE, phospholipids, and vitamin E) requires the action of the enzyme microsomal TG transfer protein (MTP). After secretion into the plasma, VLDL acquires multiple copies of apoE and apolipoproteins of the C series by transfer from HDL. The TGs of VLDL are hydrolyzed by LPL, especially in muscle and adipose tissue. Now they are referred to as IDLs, which contain roughly similar amounts of cholesterol and TG. The liver removes approximately 40–60% of IDL by LDL receptor–mediated endocytosis via binding to apoE. The remainder of IDL is remodelled by hepatic lipase (HL) to form LDL. During this process, most of the TG in the particle is hydrolyzed and all apolipoproteins except apoB-100 are transferred to other lipoproteins. Approximately 70% of circulating LDL is cleared by LDL receptor–mediated endocytosis in the liver. Lp(a) is similar to LDL in lipid and protein composition, but it contains an additional protein called Apo(a). Apo(a) is synthesized in the liver and attached to apoB-100 by a disulfide linkage. The major site of clearance of Lp(a) is the liver.

THE EXOGENOUS AND ENDOGENOUS LIPOPROTEIN METABOLIC PATHWAYS



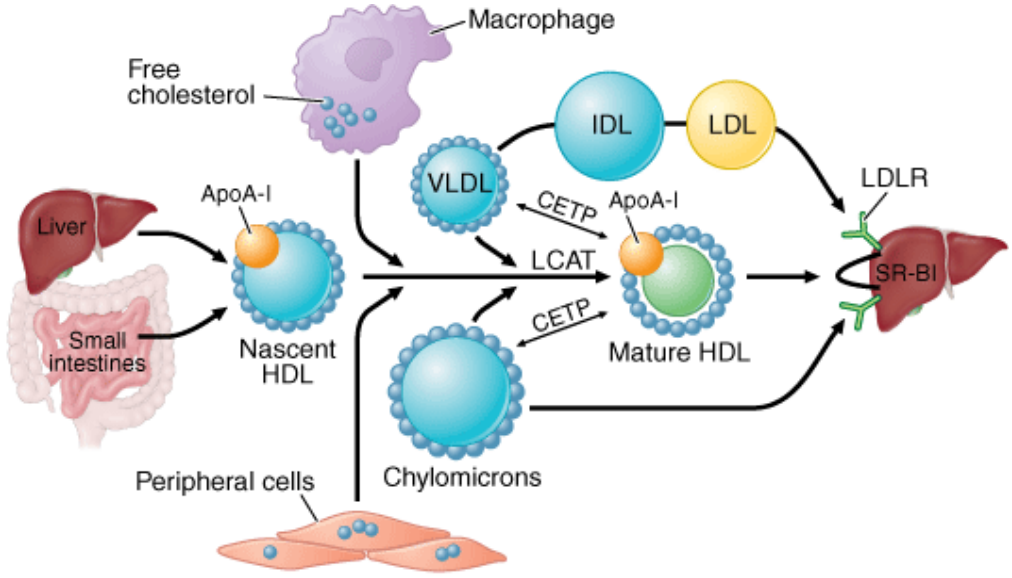
HDL METABOLISM AND REVERSE CHOLESTEROL TRANSPORT:

All nucleated cells synthesize cholesterol, but only hepatocytes and enterocytes can effectively excrete cholesterol from the body. In the liver, cholesterol is excreted into the bile, either directly or after conversion to bile acids. Cholesterol in peripheral cells is transported to the liver and intestine by a process termed "reverse cholesterol transport" that is facilitated by HDL.

Nascent HDL particles are synthesized by the intestine and the liver. Newly secreted apoA-I rapidly acquires phospholipids and unesterified cholesterol from intestine or liver, via efflux promoted by the membrane protein ATP-binding cassette protein A1 (ABCA1). This process results in the formation of discoidal HDL particles, which then recruit additional unesterified cholesterol from the periphery. Within the HDL particle, the cholesterol is esterified by LCAT, and the more hydrophobic CE moves to the core of the HDL particle. As HDL acquires more CE it becomes spherical, and additional apolipoproteins and lipids are transferred to the particles from the surfaces of chylomicrons and VLDLs during lipolysis. HDL CE can be transferred to apoB-containing lipoproteins in exchange for TG by the CE transfer protein (CETP). The CE is then removed from the circulation by LDL receptor–mediated endocytosis & also be taken up directly by hepatocytes via the scavenger receptor class BI (SR-BI).

HDL particles undergo extensive remodelling within the plasma by a variety of lipid transfer proteins and lipases. The phospholipid transfer protein has the net effect of transferring phospholipids from other lipoproteins to HDL. After CETP-mediated lipid exchange, the TG-enriched HDL becomes a much better substrate for HL, which hydrolyzes the TGs and phospholipids to generate smaller HDL particles. Endothelial lipase hydrolyzes HDL phospholipids, generating smaller HDL particles that are catabolised faster.

HDL METABOLISM AND REVERSE CHOLESTEROL TRANSPORT



FRIEDRICKSON CLASSIFICATION OF HYPERLIPOPROTEINEMIA:

TYPE	OVERNIGHT SERUM	ELEVATED PARTICLES	ASSOCIATED CLINICAL DISORDERS	SERUM TC	SERUM TG
I	Creamy top layer	Chylomicrons	Lipoprotein lipase deficiency, apolipoprotein C-II deficiency	+ to ++	++++
IIa	Clear	LDL	Familial hypercholesterolemia, polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia	++++	--
IIb	Clear	LDL,VLDL	Familial combined hyperlipidemia	+++	++
III	Turbid	Chylomicrons & VLDL remnants	Dysbetalipoproteinemia	+++	+++
IV	Turbid	VLDL	Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia	N+	++
V	Creamy top, turbid bottom	Chylomicrons & VLDL	Diabetes	+++	++++

SECONDARY DYSLIPIDEMIAS:

- **LDL-C** is **elevated** in hypothyroidism, nephrotic syndrome, cholestasis, acute intermittent porphyria, anorexia nervosa, hepatoma and drugs like thiazide & cyclosporine.
- **HDL-C** is **decreased** in smoking, type 2 DM, obesity, malnutrition, anabolic steroids and beta-blockers**.**
- **Elevated VLDL-C** is seen in obesity, type 2 DM, glycogen storage disease, hepatitis, alcohol, renal failure, sepsis, stress, cushing's syndrome, pregnancy, acromegaly, lipodystrophy and drugs like estrogen, beta blockers, glucocorticoids, bile acid binding resins & retinoic acid.
- **Lipoproteins** are **elevated** in renal insufficiency, menopause, hypothyroidism, acromegaly and drugs like growth hormone & isotretinoin.

DYSLIPIDEMIA IN CKD:

The most common dyslipidemia observed in patients with CKD is atherogenic dyslipidemia—a combination of hypertriglyceridemia, low levels of HDL-C and high levels of LDL particles[53] & Lp(a)[54]. CKD patients have a different lipid profile with increased atherogenic lipid fractions, and hence serum LDL-C levels may underestimate the atherogenic effect of in these patients. As GFR falls, TG levels increase and HDL-C falls. As proteinuria

increases, total cholesterol, LDL-C and TG all increases, whereas HDL-C decreases. Approximately 50% of HD patients and 70% of PD patients demonstrate dyslipidemia[55]. HD patients characteristically demonstrate alterations only in TG (elevated) and HDL-C (reduced) levels. In PD and transplant patients, total cholesterol, LDL-C and TG are usually higher than in the general population.

MECHANISM OF LIPID ABNORMALITIES IN CKD:

Alterations in low-density lipoprotein and cholesterol metabolism Increased LDL generation Increased apo B synthesis Increased CETP activity Increased cholesterol synthesis Increased HMG-CoA reductase activity Decreased cholesterol 7α-hydroxylase Up-regulation of hepatic ACAT Defects in LDL clearance Reduction in hepatic LDL expression Reductions in apo B catabolism
Alterations in very low density lipoprotein metabolism Impaired VLDL clearance Reduced LPL and hepatic lipase activity Reduced VLDL receptor Impaired enrichment with apo E and apo C Increased hepatic production of fatty acids and triglycerides Elevated enzymatic activity of acyl-CoA carboxylase and

fatty acid synthase Increased hepatic DGAT activity
Alterations in high-density lipoprotein Diminished LCAT activity Apo A-I enrichment of HDL Reduced expression of HDL (SR-B1) receptor
Increased Lp(a) synthesis

Though the above mechanisms are more common in nephrotic syndrome they are also proposed to play a role in CKD.

Urinary losses of albumin and LPL activators result in an increase in LDL, which in turn bind to the glomerular basement membrane further impairing its permselectivity; filtered lipoproteins accumulate in the mesangium, stimulating extracellular matrix synthesis and mesangial cell proliferation; filtered LDL is taken up and metabolized by the tubules, leading to cell injury and interstitial disease. There is also defective clearance of TG from the body.

ALTERATIONS IN LDL-C AND CHOLESTEROL METABOLISM:

Increase in LDL and total cholesterol is attributable to both increased synthesis and impaired catabolism. There is an increased absolute synthesis rate of apoB-100, the principal apoprotein constituent of LDL. Significant reductions in apoB catabolism have also been demonstrated[56]. Plasma levels and the activity of CETP which mediates the transfer of esterified cholesterol from

HDL to VLDL remnants to yield LDL are enhanced. There is also a reduced receptor-mediated LDL clearance[57].

A vicious cycle has been suggested in uremia in which the decreased catabolism of IDL and LDL leads to their increased plasma residence time and further modification of the apoB contained in these lipoproteins by oxidation, carbamylation and glycation[58]. These modifications lead to the reduced recognition and binding of these lipoproteins to LDL receptors and LRP in the liver and hence further reduction in plasma clearance by this physiologic pathway.

HYPERTRIGLYCERIDEMIA:

Plasma TGs start to increase in early stages of CKD and show the highest concentrations in nephrotic syndrome and in dialysis patients, especially those who are treated with PD. The accumulation of TG is the consequence of both a high production rate and a low fractional catabolic rate[59]. An increased production of TG rich lipoprotein is possibly a consequence of impaired carbohydrate tolerance and enhanced hepatic VLDL synthesis[60]. The reduced fractional catabolic rate is likely due to the decreased activity of LPL and hepatic lipase, which can be attributed to the depletion of enzyme pool induced by frequent heparinization in HD patients[61], an increase in the plasma apoC-III/apoC-II ratio, and the presence of other lipase inhibitors in plasma. ApoC-II is an activator of LPL, whereas apoC-III is an inhibitor of LPL. The increased

apoC-III/apoC-II ratio is usually due to a disproportionate increase in plasma apoC-III. There is also a decrease in LPL synthesis as a result of secondary hyperparathyroidism or suppressed insulin level.

ALTERATIONS IN HIGH-DENSITY LIPOPROTEIN:

Diminished activity of the LCAT & apoA1 appears to contribute to the HDL-C abnormality[62]. LCAT is involved in catalyzing the esterification of cholesterol as well as the conversion of HDL3 to HDL2. Low LCAT levels would impair this HDL maturation, in turn reducing the transfer of apoC-II to VLDL and thus inhibiting the catabolism of TG-rich lipoproteins. Increased hepatic production and elevated plasma CETP levels may contribute to HDL abnormalities[63]. Elevated CETP levels might contribute to cholesterol enrichment of TG-rich lipoproteins, as well as the observed reductions in HDL2[64]. There is a marked up-regulation of hepatic acetyl coenzyme A: cholesterol acyltransferase (ACAT) contributing to CKD induced dysregulation of HDL metabolism.

Another important component of HDL is paraoxonase, an enzyme that inhibits the oxidation of LDL. Plasma paraoxonase activity is reduced in patients with CKD[65], thereby predisposing the LDL and possibly also HDL particles to oxidation. Furthermore, infection associated or uremia associated inflammation might convert HDL from an antioxidant into a pro-oxidant particle[66]. All of these may contribute to atherogenesis in CKD.

ALTERATIONS IN VLDL-C METABOLISM:

Defective receptor-mediated clearance of VLDL owing to hepatic lipase deficiency may underlie the elevated remnant particles in nephrotic syndrome[67].

*APO*LIPOPROTEIN A – *IV (ApoA-IV):*

ApoA-IV is a 46-kDa glycoprotein that is synthesized primarily in enterocytes of the small intestine. It protects against atherosclerosis by promoting reverse cholesterol transport pathway. Specifically, apoA-IV activates LCAT and modulates the activation of LPL[68] as well as the protein-mediated transfer of CE from HDL to LDL. Cross-sectional studies have shown an inverse relationship between plasma apoA-IV levels and presence of CAD in the general population as well as in patients with CKD[69].

ApoA-IV has also been identified as a marker of primary CKD, and its plasma levels are already increased when GFR is still normal. Furthermore, high plasma apoA-IV concentrations predicts the progression of primary non-diabetic kidney disease, during a prospective 7-yr follow-up study. A tubular type of proteinuria and severe proteinuria cause a decrease in plasma apoA-IV levels[70]. In dialysis patients, apoA-IV levels are twice as high as in the general population[71].

LIPOPROTEIN(a):

Plasma Lp(a) levels are influenced by GFR. In patients with large apo(a) isoforms but not those with small apo(a) isoforms, plasma Lp(a) level begins to

increase in stage 1 CKD before GFR starts to decrease[72]. This isoform-specific increase in plasma Lp(a) levels was observed in several but not all studies in non-nephrotic patients with CKD and HD patients. In contrast, in patients with nephrotic syndrome[73] and PD patients, increases in plasma Lp(a) levels occur in all apo(a) isoform groups, probably as a consequence of the pronounced protein loss and a subsequently increased production in the liver. After successful kidney transplantation, a decrease in plasma Lp(a) can be regularly observed in HD patients with large apo(a) isoforms and in PD patients with all apo(a) isoform groups. Thus, the elevation of Lp(a) in CKD is an acquired abnormality, mostly influenced by the degree of proteinuria and less by the cause of kidney disease. Malnutrition and inflammation have also been associated with high plasma Lp(a) levels in HD patients.

PREVENTION ASPECT:

The **National Cholesterol Program (NCEP) Adult Treatment Panel (ATP) III** guidelines indicate that the upper limit of normal for total cholesterol is 240 mg/dl, LDL- C is 130 mg/dl, TG is 200 mg/dl and the lower limit for HDL- C is 35 mg/dl.

Therapeutic lifestyle changes (TLC) for dyslipidemia includes smoking cessation, diet, aerobic exercise and weight loss. The goal of the Step I NCEP diet is to reduce total cholesterol to less than 300 mg/day and in the Step II diet to less than 200 mg/day. Pharmacological management includes[74]

- HMG-CoA synthetase inhibitors
- Fibric acid derivatives for hypertriglyceridemia
    - Use with caution
    - Gemfibrozil preferred
- Niacin
- Cholesterol absorption inhibitor
    - Ezetimibe — statin-sparing
    - No controlled trials in CKD

(HMG-CoA synthetase inhibitors and fibric acid derivatives are associated with an enhanced risk of rhabdomyolysis, a risk factor for ATN).

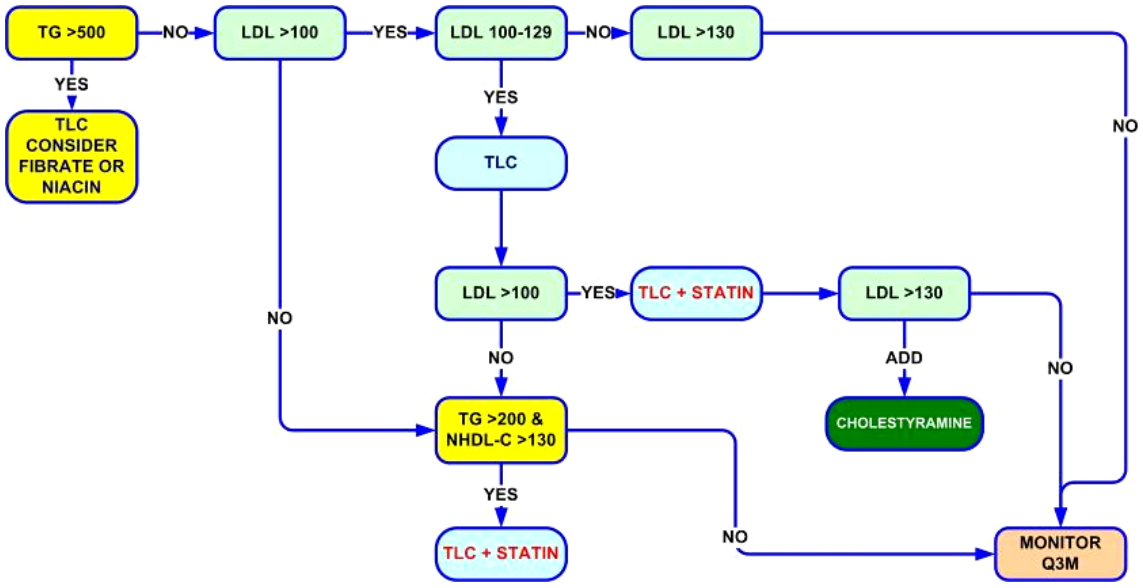
Recent data have suggested that statins have effects beyond lipid reduction and may have a beneficial anti-inflammatory and anti-fibrogenic effects[75,76], which are commonly associated with many forms of progressive renal injury such as reduction in TGF-β production and inhibition of the proliferative actions of platelet-derived growth factor[77].

The **NCEP ATP III** and **K/DOQI guidelines** recommend the below goals for treating dyslipidemia in CKD patients:

Parameter	NCEP ATP III goal	K/DOQI Revision goal
LDL-C (mg/dl)	< 130	<100
HDL-C (mg/DL)	>40	>40
TG (mg/dl)	<150	<150

In the **CARE (Cholesterol and Recurrent Events) study**, over 4,000 patients, with a subgroup of 1,700 patients with creatinine clearance <75 ml/min, with previous MI and plasma total cholesterol <240 mg/dl were randomized to pravastatin 40 mg/day or placebo and followed for approximately 5 years. These patients had a 28% (95% CI 0.55 to 0.95; p = 0.02) relative risk reduction and a 4% ARR in the primary end point (death from coronary disease or symptomatic nonfatal MI) when treated with pravastatin 40 mg/day[78].

PROTOCOL FOR TREATMENT OF DYSLIPIDEMIA



DYSLIPIDEMIA MANAGEMENT:

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG≥500 mg/dl	TG<500 mg/dl	TLC	TLC + Fibrate or niacin	Fibrate or Niacin
LDL 100-129 mg/dl	LDL<100 mg/dl	TLC	TLC + low dose Statin	Bile acid seq or Niacin
LDL≥130	LDL<100	TLC + low	TLC + max	Bile acid seq

mg/dl	mg/dl	dose Statin	dose Statin	or Niacin
TG≥200 mg/dl & non-HDL≥130 mg/dl	Non-HDL <130mg/dl	TLC + low dose Statin	TLC + max dose Statin	Fibrate or Niacin

[TLC – Therapeutic Lifestyle Changes]

The prospective randomized clinical trial - **PREVEND IT (Prevention of Renal and Vascular End Stage Disease Intervention Trial**)[79] with 864 patients with microalbuminuria were randomized to fosinopril 20 mg/day or matching placebo and to pravastatin 40 mg/day or matching placebo. Participants were followed for 4 years. Pravastatin 40 mg/day resulted in a non-significant 13% reduction (0.87 [95% CI 0.49 to 1.57]; p = 0.649) in the primary end point of cardiovascular mortality and hospitalization for cardiovascular morbidity.

In the **VA-HIT (Veterans' Affairs High-Density Lipoprotein Intervention Trial)**, over 2,500 men with CHD were enrolled and randomized to gemfibrozil 1,200 mg/day or placebo. In this study, a subgroup of 1,000 men with a creatinine clearance <75 ml/min was identified. In post hoc analysis, these patients with mild to moderate CKD were found to have a 27% relative risk reduction (0.73 [95% CI 0.56 to 0.96]; p = 0.02) and a 6.3% absolute risk reduction in fatal and nonfatal MI[80].

Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm

(ASCOT-LLA) showed a lower rate of the primary end point of nonfatal MI and fatal CHD in those patients with relatively mild renal dysfunction[81].

UK Heart and Renal Protection study (UK-HARP-I) used simvastatin 20 mg/d which lowered LDL cholesterol by 26% in CKD patients.

The **Study of Heart and Renal Protection (SHARP)** is a large-scale, randomized, placebo-controlled trial designed to evaluate the effects of cholesterol-lowering treatment with simvastatin (20 mg/day) plus ezetimibe (10 mg/day) on major cardiovascular events in patients with CKD without known CVD. This study had 9000 patients: 6000 with CKD (serum creatinine >1.5 mg/dl in women and 1.7 mg/dl in men) and 3000 on dialysis. The primary outcome was the time to a first cardiovascular event to occur, defined as a composite of MI, cardiac death, stroke, or coronary or non-coronary revascularization. Progression of renal disease was a secondary outcome of the study.

According to ATP III, 79.8% of a cross-sectional group of ESRD pts in the **Dialysis Morbidity and Mortality Study (DMMS)**[82] had dyslipidemia.

In a study conducted by **B Shah, S Nair, et al., in Nephrology Section, PD Hinduja National Hospital's Research Centre, Mahim, Bombay**[83], it was observed that

- CKD patients on *conservative treatment* had *TG* significantly elevated (mean=222.78 mg/dl) when compared to the other groups (HD, post-transplant & control).

- The most common lipid abnormality observed in *renal transplant patients is hypercholesterolemia* (37.5%). The mean total cholesterol in post transplant was 217 mg/dl, followed by the group on conservative treatment (mean=211.33 mg/dl). Those on HD had mean total cholesterol (163.37 mg/dl) which was less than that of the normal controls (184.11 mg/dl). But the differences in the total cholesterol between these groups were not statistically significant.
- A decrease in HDL-C or increase in LDL-C was not noticed in the CKD group when compared with the controls.
- A lower Apo A1/Apo B ratio was present in CKD patients on HD ($p<0.001$) and in those on conservative management ($p<0.01$).

According to a study conducted by **A. Madhusudhana Rao, et al., on lipid abnormalities, lipoprotein (a) and apoprotein pattern in non-dialyzed patients with CKD**[84], among the various parameters tested, *TGs were high in CKD stage 1-4* ($p<0.05$), whereas *VLDL-C was significantly high ($p<0.05$) in all the groups* when compared to controls. However, *LDL-C was significantly low in stage 5* only, as compared to control group ($P<0.05$). Though total cholesterol levels in stage 1 & 2 and LDL levels in stage 1-4 were higher than controls, the values attained were not statistically significant ($P>0.05$). HDL-C was lower in stage 5 CKD, but not significant.

Data from **National Health and Nutrition Examination Survey (NHANES) III and the Framingham Offspring Study, Data from multiple**

observational studies kasiske[85] & study in Singapore General Hospital conducted by **CM Chan, Department of Renal Medicine reported in Ann Acad Med**[86], showed the below lipid abnormalities:

	Total Cholesterol >240 mg/dl	LDL Cholesterol >130 mg/dl	HDL Cholesterol <35 mg/dl	Triglycerides >200 mg/dl
General population	20%	40%	15%	15%
With nephrotic syndrome	90%	85%	50%	60%
Without nephrotic syndrome	30%	10%	35%	40%
Hemodialysis	20%	30%	50%	45%
Peritoneal dialysis	25%	45%	20%	50%

Prevalence of dyslipidemia, by guideline definitions, was 82%, predominantly manifested by elevated triglycerides (52%) and VLDL (52%) and decreased HDL (51%), with less frequent elevations of LDL (40%) and total cholesterol (24%), according to a study by **Pennell P, et al., Division of Nephrology and Hypertension (R-126), Miller School of Medicine, University of Miami in University of Miami**[87].

In all of the above studies, CKD group was selected irrespective of the etiology. No exclusion for diabetes was made. In one study from **Department of Hemodialysis and Renal Transplantation, Victor Babes University of**

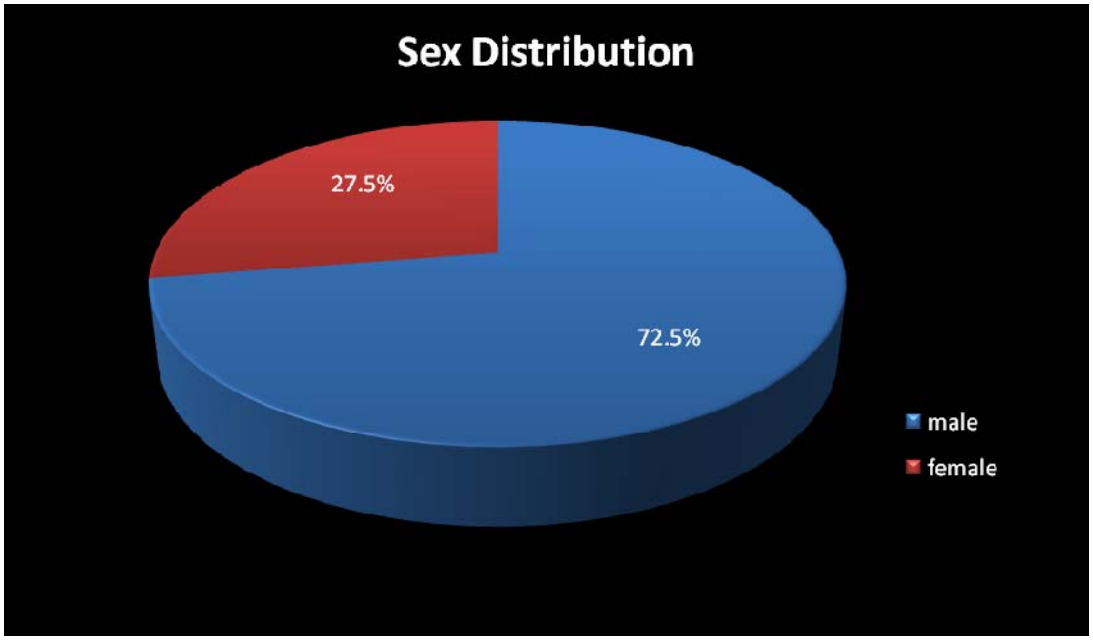
Medicine and Pharmacy, Timisoara[88], an increase in TGs & decrease in HDL-C were noted in diabetic CKD as opposed to non diabetic CKD. *LDL-C was increased in non-diabetic CKD*. Diabetic patients without CKD had a higher TG & lower HDL-C when compared with non-diabetic CKD, which means diabetes possess higher dyslipidemic potency when compared with CKD per se.

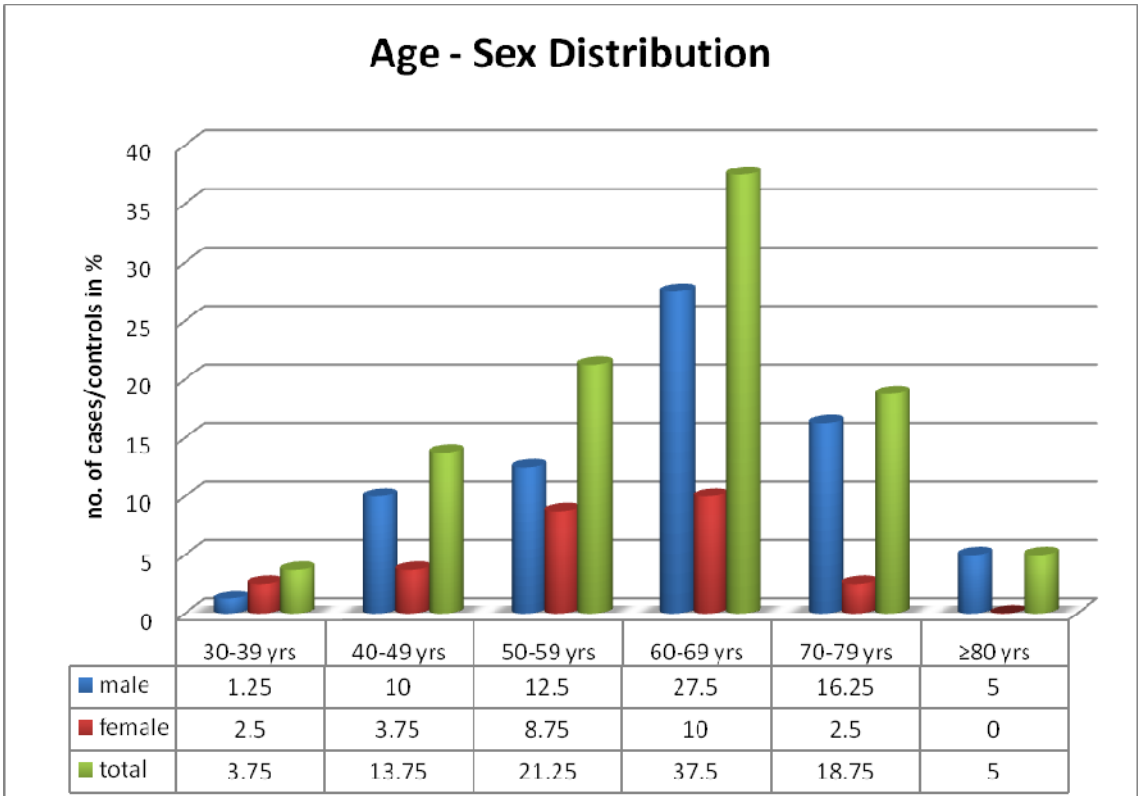
RESULTS & ANALYSIS

1) DISTRIBUTION OF STUDY GROUP ACCORDING TO AGE & SEX:

AGE DISTRIBUTION (in yrs)	MALE		FEMALE		TOTAL	
	no	%	no	%	no	%
30-39	1	1.25	2	2.50	3	3.75
40-49	8	10.00	3	3.75	11	13.75
50-59	10	12.50	7	8.75	17	21.25
60-69	22	27.50	8	10.00	30	37.50
70-79	13	16.25	2	2.50	15	18.75
≥80	4	5.00	0	0	4	5.00
TOTAL	58	72.5	22	27.5	80	100

Among the 80 cases and their age & sex matched controls, 72.5 % (58) are males and 27.5% (22) are females.





	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs	≥80 yrs
male	1.25	10	12.5	27.5	16.25	5
female	2.5	3.75	8.75	10	2.5	0
total	3.75	13.75	21.25	37.5	18.75	5

In the study group & their age - sex matched controls, 37.5% were in the 60-69 yrs of age group. Next majority was in the 50-59 yrs age group (21.25%), followed by 70-79 yrs (18.75%), 40-49 yrs (13.75%), above 80 yrs (5%) and 30-39 yrs (3.75%).

Among males, most of them were between 60-69 yrs (27.5%), followed by 70-79 yrs (16.25%), 50-59 yrs (12.5%), 40-49 yrs (10%), above 80 yrs (5%) and lastly 30-39 yrs (1.25%).

Among females, most of them were between 60-69 yrs (10%), followed by 50-59 yrs (8.75%), 40-49 yrs (3.75%). 30-39 yrs and 70-79 yrs formed 2.5% each. There were no females above 80 yrs in the study & control group.

2) COMPARISON OF BMI, UREA, CREATININE & CREATININE CLEARANCE AMONG STUDY AND CONTROL POPULATION:

CRITERIA	CONTROL			STUDY			MEAN DIFFERENCE	SE DIFFERENCE	P VALUE	
	n	Mean	S.D	n	Mean	S.D				
BMI	80	22.44	1.74	80	21.26	2.35	1.18	0.32	.0001	Sig
UREA (mg/dl)	80	28.40	5.04	80	106.49	41.23	78.09	4.64	.0001	Sig
CREATININE (mg/dl)	80	0.91	0.11	80	5.61	3.33	4.71	0.373	.0001	Sig
CREATININE CLEARANCE (ml/min)	80	68.07	8.44	80	13.79	7.31	54.28	1.24	.0001	Sig

The mean BMI in the study group was 21.26 whereas that among the control was 22.44 and this difference was significant (p=0.0001; 95% CI 0.54 to 1.83).

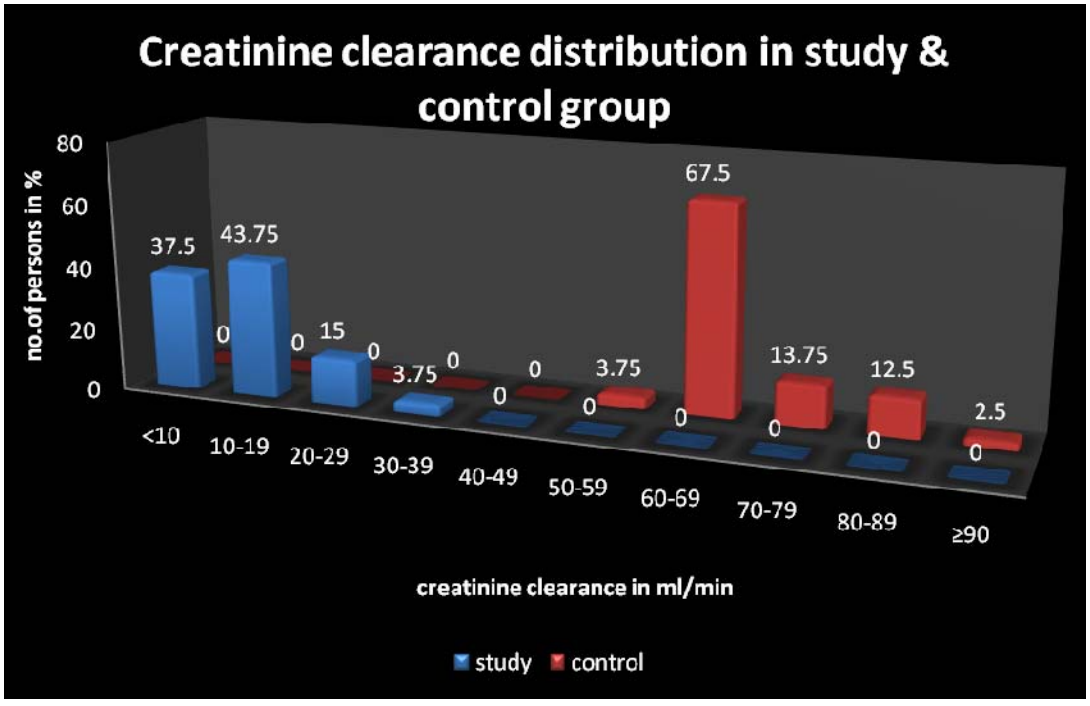
The mean urea in the study group was 106.49 mg/dl & that in the control was 28.4 mg/dl, which is a significant difference (p=0.0001; 95% CI -87.33 to -68.85).

The mean creatinine in the study group was 5.61 mg/dl & that in the control was 0.91 mg/dl and this difference is significant (p=0.0001; 95% CI -5.45 to -3.96).

The mean creatinine clearance in the study group was 13.79 ml/min & that in the control was 68.07 ml/min (p=0.0001; 95% CI 51.81 to 56.75).

3) DISTRIBUTION OF CREATININE CLEARANCE AMONG STUDY GROUP AND CONTROL POPULATION:

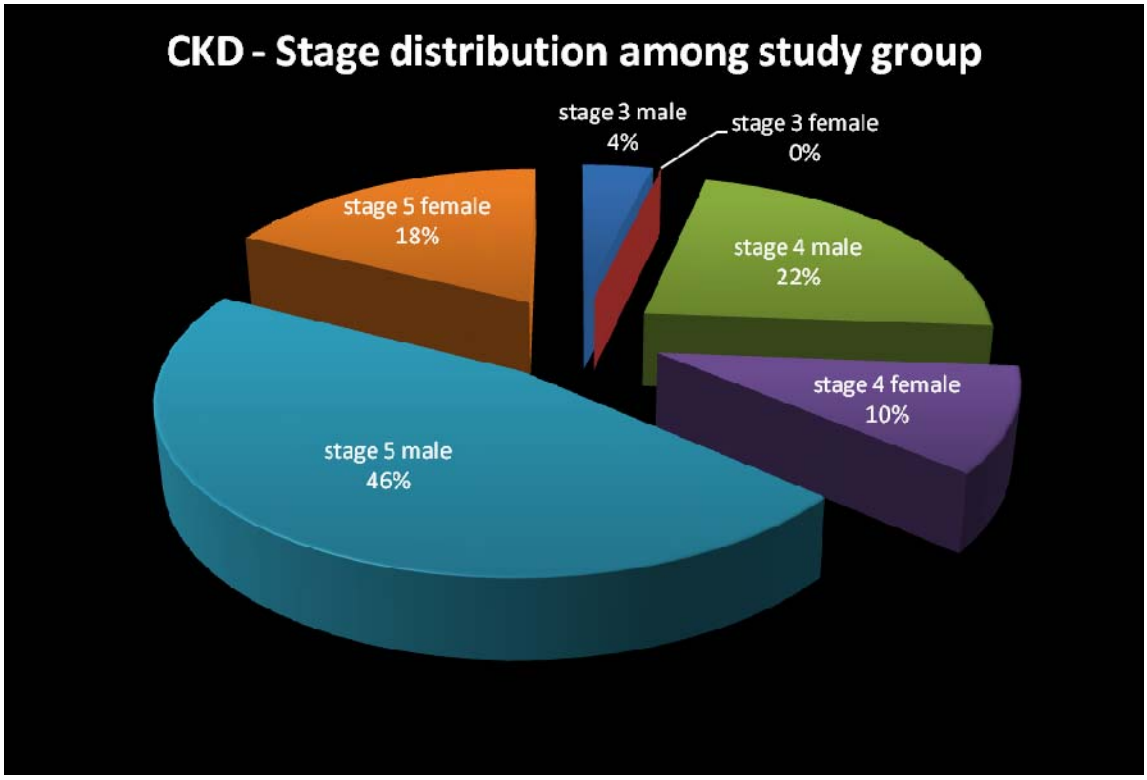
CREATININE CLEARANCE (ml/min)	STUDY		CONTROL	
	NO	%	NO	%
<10	30	37.5	0	0
10-19	35	43.75	0	0
20-29	12	15	0	0
30-39	3	3.75	0	0
40-49	0	0	0	0
50-59	0	0	3	3.75
60-69	0	0	54	67.5
70-79	0	0	11	13.75
80-89	0	0	10	12.5
≥90	0	0	2	2.5
TOTAL	80	100	80	100



In the study group the creatinine clearance was below 39 ml/min and most of them had creatinine clearance below 19 ml/min. In the control population it was above 50 ml/min.

4) STAGING OF CKD AMONG STUDY GROUP - SEX WISE:

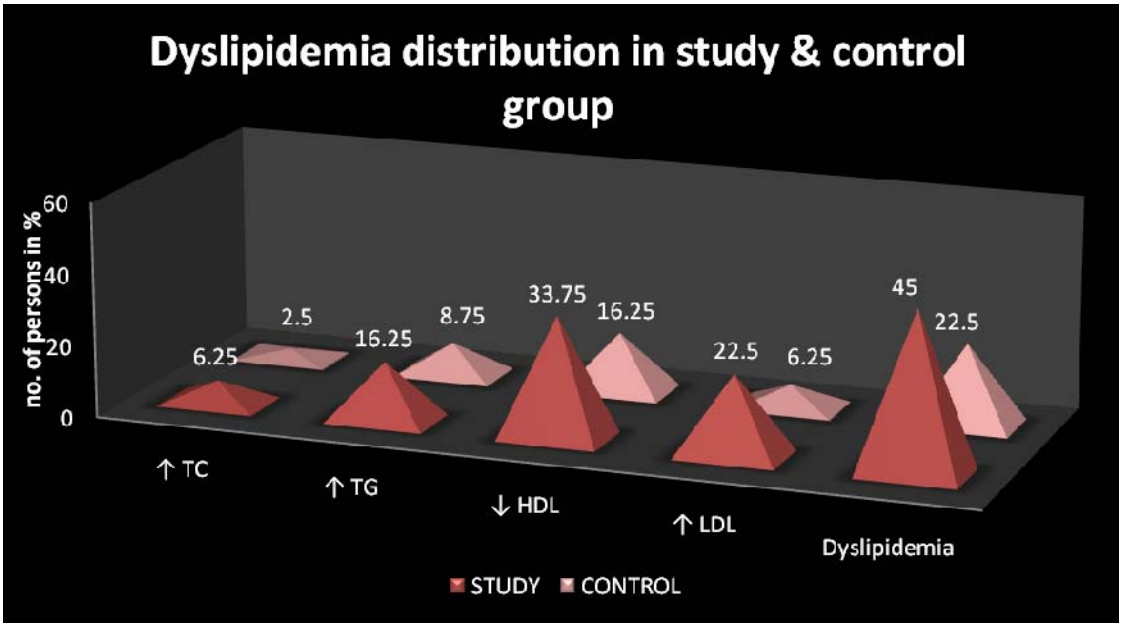
	MALE		FEMALE		TOTAL	
STAGE	**NO**	**%**	**NO**	**%**	**NO**	**%**
3	3	3.75	0	0	3	3.75
4	18	22.5	8	10	26	32.5
5	37	46.25	14	17.5	51	63.75
TOTAL	58	72.5	22	27.5	80	100



Most of the CKD cases were in stage 5 (63.75%). This distribution was maintained both in males & females. This was followed by stage 4 (32.5%) and then stage 3 (3.75%).

5) DISTRIBUTION OF LIPID ABNORMALITIES AMONG STUDY & CONTROL GROUP:

LIPID ABNORMALITY	STUDY		CONTROL		ODDS RATIO	95% CI
	NO	%	NO	%		
↑ TC	5	6.25	2	2.5	2.60	0.49 - 13.81
↑ TG	13	16.25	7	8.75	2.02	0.76 – 5.37
↓ HDL	27	33.75	13	16.25	2.62	0.18 – 0.81
↑ LDL	18	22.50	5	6.25	4.36	1.53 – 12.40
Dyslipidemia	36	45	18	22.5	2.82	-



In the study group, there was an increase in the total cholesterol, triglycerides & LDL and decrease in HDL when compared with the control population and the difference was significant by odds ratio (odds ratio > 1).

Dyslipidemia (defined as presence of one or more lipid abnormalities) was present in 36 of the study group (45%) and 18 in the control group (22.5%) which was also significant by odds Ratio (2.82).

6) COMPARISON OF TOTAL CHOLESTEROL, TRIGLYCERIDES, HDL, TC/HDL, LDL-C & VLDL AMONG STUDY AND CONTROL POPULATION:

CRITERIA	CONTROL			STUDY			MEAN DIFFERENCE	STD. ERROR DIFFERENCE	P VALUE	
	n	Mean	S.D	n	Mean	S.D				
TC	80	155.43	27.51	80	170.80	46.54	15.38	6.04	.012	**Sig**
TG	80	136.80	30.00	80	154.15	67.58	17.35	8.26	.037	**Sig**
HDL	80	38.50	3.579	80	37.15	4.93	1.35	0.68	.049	**Sig**
TC/HDL	80	4.08	0.88	80	4.71	1.52	0.63	0.19	.002	**Sig**
LDL-C	80	89.68	26.46	80	101.60	44.41	11.93	5.78	.041	**Sig**
VLDL	80	27.25	6.02	80	30.21	12.58	2.96	1.56	.059	**Not sig**

When compared with the control group, the study population had significantly increased total cholesterol (p=0.012), triglycerides (p=0.037), LDL-C (p=0.041) and TC/HDL ratio (p=0.002) and the decrease in the HDL-C was also significant (p=0.049) when compared with the control group. Whereas, there was an increase in VLDL-C in the study population when compared with the control group, but this increase was not significant (p=0.059).

7) ANALYSIS OF LIPID ABNORMALITIES AMONG STUDY AND CONTROL POPULATION:

CRITERIA	CONTROL			STUDY			MEAN DIFFERENCE	STD. ERROR DIFFERENCE	P VALUE	
	n	Mean	S.D	n	Mean	S.D				
↑ TC	2	242.00	.000	5	293.40	52.28	51.40	39.12	0.246	Not Sig
↑ TG	7	214.71	11.87	13	272.85	73.46	58.13	28.30	0.015	Sig
↓ HDL	13	33.31	0.95	27	31.70	1.88	1.60	0.55	0.006	Sig
↑ LDL-C	5	149.40	13.61	18	162.88	41.98	13.49	19.33	0.493	Not Sig

On considering only the dyslipidemia population in both the study and control group, 36 in the study group (45%) had dyslipidemia and 18 in the control group (22.5%) had dyslipidemia.

On analysing the above population alone, there was an increase in the prevalence of ↑TC & LDL-C but this increase was not statistically significant ($p>0.05$).But the decrease in HDL-C and increase in TGs in the study group were statistically significant when compared with the controls ($p=0.006$ & $p=0.015$, respectively).

8) CKD STAGE WISE ANALYSIS OF LIPID ABNORMALITIES:

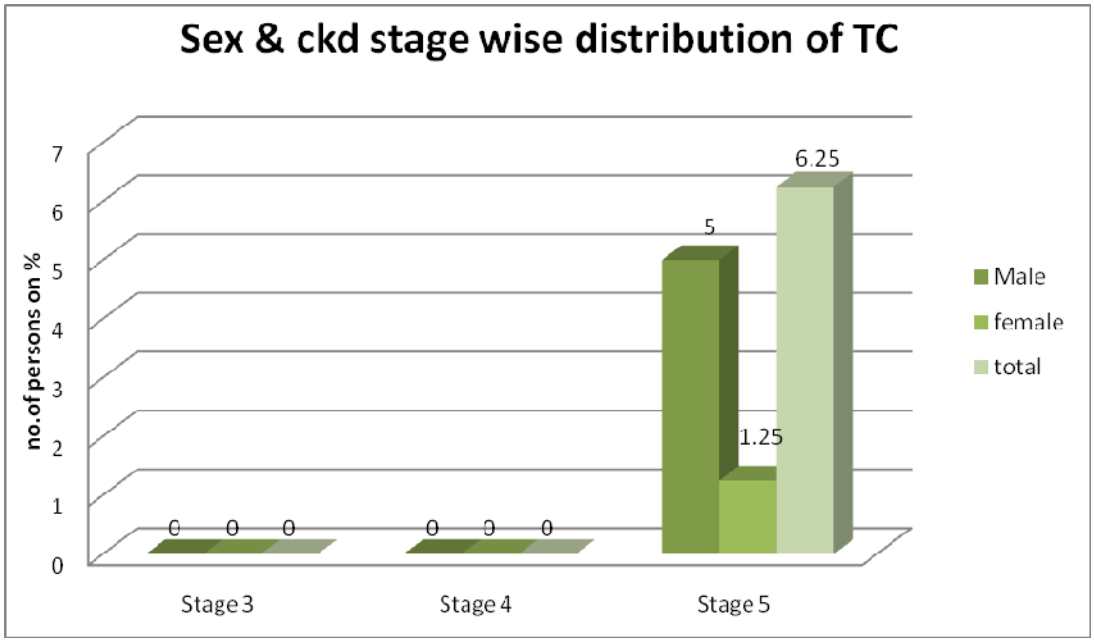
CRITERIA	STAGE 3	STAGE 4	STAGE 5
↑ TC	0 %	0%	6.25%
↑ TG	0%	7.5%	8.75%
↓ HDL-C	0%	12.5%	21.25%
↑ LDL-C	0%	6.25%	16.25%
DYSLIPIDEMIA	0%	46.15%	47.06%

In stage 3 CKD, no lipid abnormalities were noticed. In stage 4 & 5, dyslipidemia (defined as presence of one or more lipid abnormalities) was 46.15% and 47.06% respectively.

Total cholesterol was within the normal limits in stage 4 CKD group, whereas it was elevated in stage 5. The increase in TGs & LDL-C and decrease in HDL-C were higher in stage 5 when compared with stage 4.

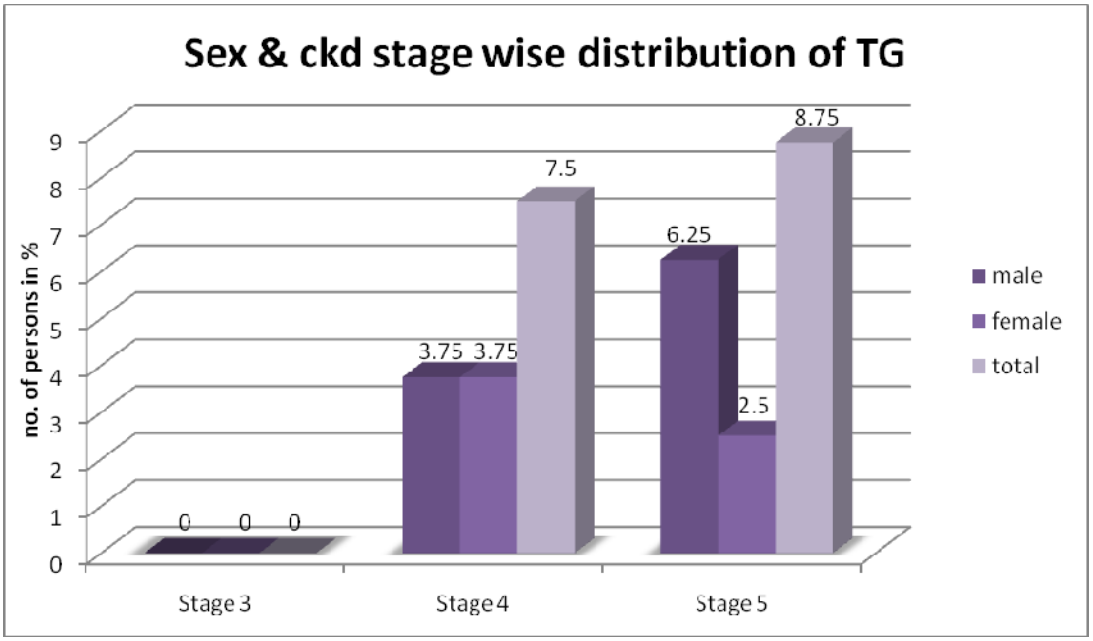
9) SEX & CKD STAGE WISE DISTRIBUTION OF INCREASED TOTAL CHOLESTEROL:

CKD-STAGE	MALE		FEMALE		TOTAL	
	NO	%	NO	%	NO	%
3	0	0	0	0	0	0
4	0	0	0	0	0	0
5	4	5	1	1.25	5	6.25



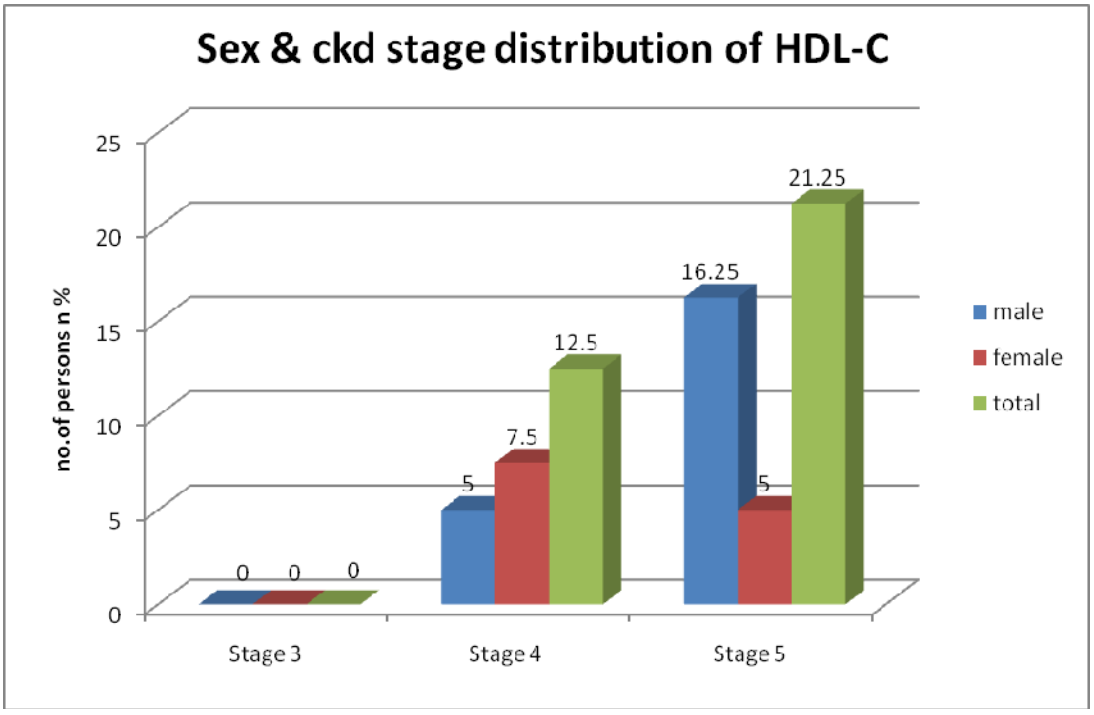
10) SEX - WISE DISTRIBUTION OF TRIGLYCERIDES AMONG DIFFERRENT STAGES OF CKD:

CKD-STAGE	MALE		FEMALE		TOTAL	
	NO	%	NO	%	NO	%
3	0	0	0	0	0	0
4	3	3.75	3	3.75	6	7.5
5	5	6.25	2	2.5	7	8.75



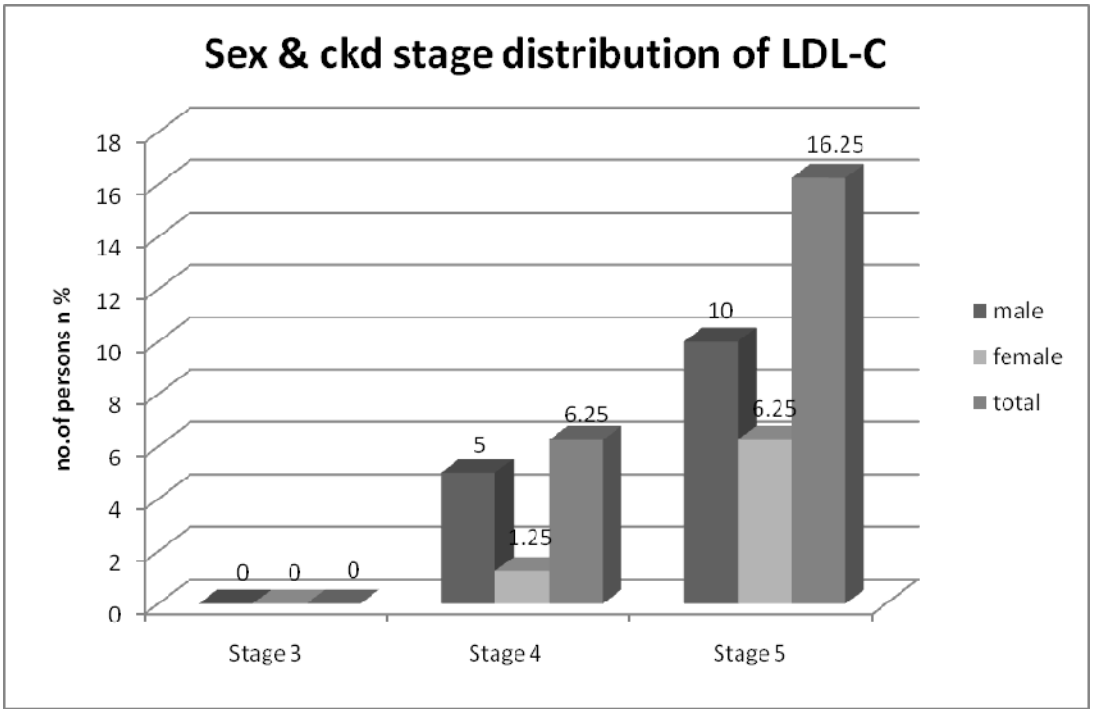
11) SEX - WISE DISTRIBUTION OF HDL-C AMONG DIFFERRENT STAGES OF CKD:

CKD-STAGE	MALE		FEMALE		TOTAL	
	NO	%	NO	%	NO	%
3	0	0	0	0	0	0
4	4	5	6	7.5	10	12.5
5	13	16.25	4	5	17	21.25



12) SEX - WISE DISTRIBUTION OF LDL-C AMONG DIFFERRENT STAGES OF CKD:

CKD-STAGE	MALE		FEMALE		TOTAL	
	NO	%	NO	%	NO	%
3	0	0	0	0	0	0
4	4	5	1	1.25	5	6.25
5	8	10	5	6.25	13	16.25



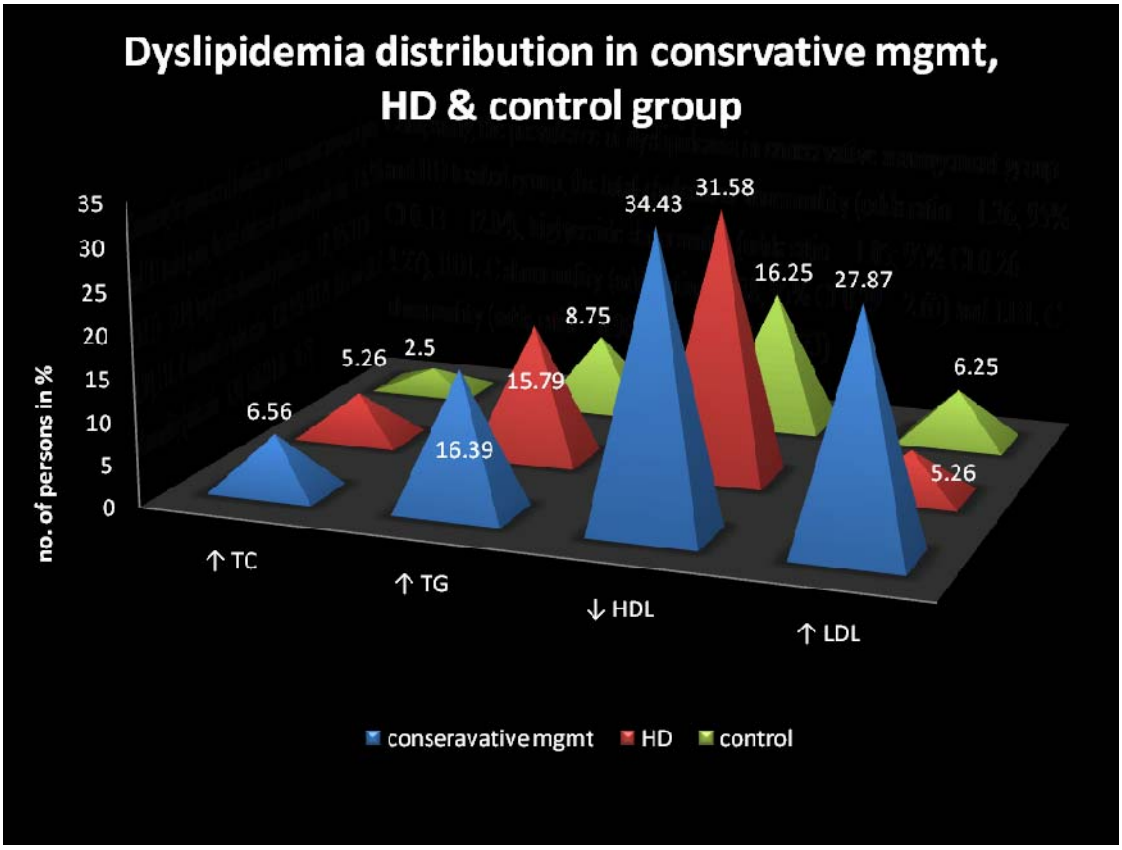
13) COMPARISON OF TC, TG, HDL, TC/HDL, LDL-C & VLDL IN STUDY GROUP BETWEEN THOSE ON HEMODIALYSIS AND THOSE ON CONSERVATIVE MANAGEMENT:

CRITERIA	HD			CONSERVATIVE MGMT			MEAN DIFFERENCE	STD. ERROR DIFFERENCE	P VALUE	
	n	Mean	S.D	n	Mean	S.D				
TC	19	150.21	39.72	61	177.21	46.93	27.00	11.92	0.018	**Sig**
TG	19	149.58	85.86	61	155.57	61.58	5.99	17.86	0.738	**Not Sig**
HDL	19	35.79	3.82	61	37.57	5.18	1.78	1.29	0.113	**Not Sig**
LDL-C	19	85.68	31.46	61	106.56	46.85	20.87	11.50	0.073	**Not Sig**
VLDL	19	28.74	16.41	61	30.67	11.26	1.94	3.32	0.562	**Not Sig**
TC/HDL	19	4.28	1.43	61	4.84	1.53	0.56	0.39	0.162	**Not Sig**

A comparison was made between the lipid status of the study group on conservative treatment and those on haemodialysis (HD). The analysis showed that the TG, LDL-C, VLDL & TC/HDL were higher in the conservatively managed group when compared with the HD group, but was not statistically significant ($p>0.05$). The total cholesterol level in the conservatively managed group was higher when compared with the HD group and this increase was statistically significant ($p=0.018$). The HDL-C was lower in the conservatively managed group when compared with the HD group, but was not statistically significant ($p>0.05$).

In the **HD group** (n=19), the prevalence of dyslipidemia was **31.58%** (6 patients had dyslipidemia), whereas in the **conservatively managed** group (n=61), the prevalence was **49.18%** (30 patients had dyslipidemia).

LIPID ABNORMALITY	CONSERVATIVE MGMT			HD			CONTROL		
	n	NO	%	n	NO	%	n	NO	%
↑ TC	61	4	6.56	19	1	5.26	80	2	2.5
↑ TG	61	10	16.39	19	3	15.79	80	7	8.75
↓ HDL	61	21	34.43	19	6	31.58	80	13	16.25
↑ LDL	61	17	27.87	19	1	5.26	80	5	6.25



DISCUSSION

CKD is a worldwide health problem and one of the growing, silent epidemic of non-communicable diseases. For a long time, dyslipidemia in CKD patients was an underestimated problem. Diabetes, nephrotic syndrome, thiazide diuretics and many secondary causes of dyslipidemia are well known to us and obviously CKD due to the above disorders (diabetes being the most common etiology) will have dyslipidemia. This study was hence undertaken to look, whether chronic kidney disease per se, possess a risk of dyslipidemia (without the above secondary causes of dyslipidemia) by excluding obesity, diabetes, patients with nephrotic range of proteinuria, those on beta-blockers & OCPs, pregnant patients, patients with history of smoking and chronic alcohol intake.

80 such CKD patients were selected (who satisfied the above exclusion & inclusion criteria) and 80 age and sex matched, hospital based controls were also chosen and lipid profile was done on a fasting sample. The results obtained were statistically analysed.

In this study of 80 patients, **males predominated (72.5%)** compared to females (27.5%). Majority of the *males* were in the age group of *60-79 yrs*, whereas *females* were in the age group of *50-69 yrs*.

The *mean BMI of the study group was significantly lower* (21.26) than that of the control group (22.44) (p=0.0001). This may be probably due to

malnourishment of the CKD patients. The *mean blood urea level in the study group was 106.49 mg/dl & that in the control was 28.4 mg/dl*, which is a significant difference (p=0.0001). The *mean creatinine in the study group was 5.61 mg/dl* & that in the control was 0.91 mg/dl and this difference is also significant (p=0.0001).

The *mean creatinine clearance in the study group was 13.79 ml/min* & that in the control was 68.07 ml/min, which again was significant. In the study group the creatinine clearance was *below 39 ml/min* and *most of them had it less than 19 ml/min*. In the control population it was above 50 ml/min and most of them had above 60 ml/min.

The CKD patients were staged according to Kidney Disease Outcomes Quality Initiative **(K/DOQI 2002)** guidelines. Only 3.75% of them were in stage 3; 32.5% were in stage 4 & majority (63.75%) in stage 5. This distribution was maintained both in males & females.

There was an **increase in the prevalence of total cholesterol abnormality** (6.25% in study group Vs 2.5% in controls), **triglyceride abnormality** (16.25% Vs 8.75%), **LDL-C abnormality** (22.5% Vs 6.25%) & **HDL-C abnormality** (33.75% Vs 16.25**%) in the study group**, when compared with the control group (odds ratio > 1). Dyslipidemia (defined as presence of one or more lipid abnormalities) was present in 36 of the study group (45%) and 18 in the control group (22.5%) (odds ratio=2.46).

Comparing this data with the **Data from National Health and Nutrition Examination Survey (NHANES) III and the Framingham Offspring Study , Data from multiple observational studies kasiske**[85] & study in Singapore General Hospital conducted by **CM Chan, Department of Renal Medicine reported in Ann Acad Med**[86],

	TC >240 mg/dl	**LDL-C >130 mg/dl**	**HDL-C <35 mg/dl**	**TG >200 mg/dl**
Control-NHANES III	20%	40%	15%	15%
Control-this study	2.5%	6.25%	16.25%	8.75%
CKD without nephrotic syndrome-conservative mgmt-NHANES III	30%	10%	35%	40%
CKD without DM & Nephrotic proteinuria-conservative mgmt-this study	6.56%	27.87%	34.43%	16.39%
HD-NHANES III	20%	30%	50%	45%
HD-this study	5.26%	5.26%	31.58%	15.79%

The prevalence of all the lipid abnormalities in this study were higher in the CKD population than the controls, the most significant being increased prevalence of total cholesterol & LDL-C. In the above NHANES III study, *the prevalence of LDL-C abnormality in CKD population was lower than that in the control group and the main abnormality was increased TGs.*

Comparing this study with the NHANES III study, the prevalence of total cholesterol and LDL-C abnormality is much lower in our population, even in the *control group*. The prevalence of increased triglycerides is half that of western population in the normal control group, whereas the prevalence of HDL-C abnormality is slightly higher than that of the western population. **Comparing our study population on conservative treatment with that of the NHANES III** (who has also excluded nephrotics in their study group but not DM or other secondary causes of dyslipidemia), the **prevalence of increased LDL-C was twice higher** than that of the western group. But the **prevalence of total cholesterol & TG abnormality was much lesser**. The prevalence of *HDL-C abnormality is almost equal in both the groups.*

Comparing our study population on HD with that of the NHANES III group, the prevalence of all the lipid abnormalities were lower.

When compared with the control group, the study population had significantly increased total cholesterol (p=0.012), triglycerides (p=0.037), LDL-C (p=0.041) and TC/HDL ratio (p=0.002) and the decrease in the HDL-C was also significant (p=0.049) when compared with the control group. Whereas there was an increase in VLDL-C in the study population when compared with the control group, but this increase was not significant (p=0.059).

Comparing this study with a study conducted by **B Shah, S Nair, et al., in Nephrology Section, PD Hinduja National Hospital's Research Centre, Mahim, Bombay**[83], following was observed:

Parameters (mean) (mg/dl)	Control-Bombay study	Control-this study	CKD-conservative mgmt-Bombay study	CKD-conservative mgmt-this study	CKD-HD-Bombay study	CKD-HD-this study
TC	184.11	155.43	211.33	177.21*	163.37	150.21*
HDL-C	44.22	38.50	52.69	37.57*	49.37	35.79
LDL-C	114.33	89.68	109.63	106.56*	89.84	85.68
TG	127.78	136.80	222.78*	155.57*	121.16	149.58

(* - $p<0.05$)

The control population of the **Bombay study** had a higher TC, LDL-C and HDL-C & a lower TG when compared with our control population. The **conservatively managed CKD group had TC and TG abnormality** when compared with the control and the HD population. **Those on HD** had a lower TC, LDL-c & TGs, but the **HDL-C abnormality** was noticed ($p>0.05$).

In **our study**, **conservatively managed group** had an **abnormality in the TC, HDL-C, LDL-C & TGs** when compared with the control group ($p<0.05$). Comparing it with the conservatively managed group of the Bombay study, all the lipid parameters were lower. In the **HD group**, TC, LDL-C, TGs, VLDL-C & TC/HDL ratio were lower than the conservatively managed group, but **p value was significant only for TC**. **HDL-C was low in the HD group** than in the conservative management group, but not significant [$p=0.17$].

In the **HD group** (n=19), the prevalence of dyslipidemia was **31.58%** (6 patients had dyslipidemia), whereas in the **conservatively managed** group (n=61), the prevalence was **49.18%** (30 patients had dyslipidemia).

In addition in our study, TC/HDL ratio was higher in the study group (4.71) than the controls (4.01) which was significant (p=0.002). VLDL-C was also elevated in the study group but not significant (p=0.059).

In stage 3 CKD, no lipid abnormalities were noticed. The prevalence of increase in TGs & LDL-C and decrease in HDL-C were higher in stage 5 when compared with stage 4. In stage 4 & 5, dyslipidemia (defined as presence of one or more lipid abnormalities) was 46.15% and 47.06% respectively.

According to a study conducted by **A. Madhusudhana Rao, et al., on lipid abnormalities, lipoprotein(a) and apoprotein pattern in non-dialyzed patients with CKD**[106], *TGs were high in CKD stage 1-4* ($p<0.05$), whereas *VLDL-C was significantly high ($p<0.05$) in all the groups* when compared to controls. However, *LDL-C was significantly low in stage 5* only as compared to control group ($P<0.05$). Though total cholesterol levels in stage 1 & 2 and LDL levels in stage 1-4 were higher than controls, the values attained were not statistically significant ($P>0.05$). HDL-C was lower in stage 5 CKD, but not significant.

Prevalence of dyslipidemia, by guideline definitions, was 82%, predominantly manifested by elevated triglycerides (52%) and VLDL (52%) and decreased HDL (51%), with less frequent elevations of LDL (40%) and

total cholesterol (24%), according to a study by **Pennell P, et al., Division of Nephrology and Hypertension (R-126), Miller School of Medicine, University of Miami in University of Miami**[87].

In all of the above studies, CKD group was selected irrespective of the etiology. No exclusion for diabetes was made. In one study from **Department of Hemodialysis and Renal Transplantation, Victor Babes University of Medicine and Pharmacy, Timisoara**[88], the increase in TGs & decrease in HDL-C was noticed in diabetic CKD as opposed to non diabetic CKD. LDL-C was increased in non diabetic CKD. Diabetic patients without CKD had a higher TG & lower HDL-C when compared with non-diabetic CKD, which means diabetes possess higher dyslipidemic potency when compared with CKD per se.

Concluding, hypertriglyceridemia and elevated total cholesterol was the main abnormality in CKD patients on conservative management in other studies, this study shows significant elevation of total cholesterol, triglycerides, LDL-C and decreased HDL-C. In the hemodialysis group of other studies, total cholesterol, triglycerides, LDL-C and HDL-C were decreased, but not significant. Similar results were noted in this study too, with decrease in total cholesterol alone being significant. So chronic kidney disease per se, excluding the other causes of secondary dyslipidemia, possess lipid abnormalities.

CONCLUSION

This case - control study was aimed at finding out the prevalence and type of dyslipidemia in chronic kidney disease excluding the secondary causes of dyslipidemia like obesity, diabetes, nephrotic syndrome, beta-blocker intake, pregnant patients, etc., and comparing it with the age & sex matched controls. On analysis,

a) There was an increase in the prevalence of dyslipidemia (elevated total cholesterol, LDL-C, triglycerides, VLDL-C & TC/HDL ratio and decreased HDL-C), as defined by the National Cholesterol Program (NCEP) Adult Treatment Panel (ATP) III guidelines.

b) The major lipid abnormalities in the CKD population were elevated total cholesterol, triglycerides &LDL-C and decreased HDL-C.

c) No lipid abnormality was noted in stage 3 CKD. In stage 4, there was an increase in triglycerides & LDL-C and decrease in HDL-C, while in stage 5 there was an increase in total cholesterol, triglycerides & LDL-C and decrease in HDL-C.

d) On comparing the conservatively managed group with the hemodialysis group, the prevalence of dyslipidemia was lower. Total cholesterol was significantly lower in hemodialysis population, but decrease in triglycerides, LDL-C, HDL-C and VLDL-C were not significant.

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PROFORMA

1. Name:

2. Age: 3. Sex:

4. OP number: Date:

5. IP number: Date of admission:

6. Chief complaints:

7. Diagnosis:

8. Past history: a) hypertension:

b) PD/HD:

General examination:

9. PR: /min. 10. BP: mmHg.

11. Height: m. 12. Weight: Kg.

13. BMI: 14. Pallor:

Systemic examination:

15. CVS:

16. RS:

17. Abdomen:

18. CNS:

19. Eye - fundus:

Investigations:

20. Hemoglobin: g/dl

21. Blood sugar : mg/dl 22. Blood urea: mg/dl

23. S.creatinine: mg/dl

24. Creatinine clearance (calculated): ml/min

25. Electrolytes (mEq/L): Na: K: Cl: HCO3:

26. USG Abdomen:

27. Fasting Lipid Profile:

a) Total cholesterol: mg/dl b) TG: mg/dl

c) HDL: mg/dl d) LDL: mg/dl

e) VLDL: mg/dl e) TC/HDL ratio:

28. ECG:

29. Urine analysis:

CONTROL

S.NO	NAME	AGE	SEX	HEIGHT (cm)	WEIGHT (Kg)	BMI	FBS (mg/dl)	PP (mg/dl)	UREA (mg/dl)	CREATININE (mg/dl)	CREATININE CLEARANCE (ml/min)	T CHOL (m
1	MURUGESAN	60	M	150	55	24.44	81	115	23	0.9	67.90	
2	MURUGAN	32	M	159	60	23.73	88	124	29	1.0	90.00	
3	VELLAYAN	40	M	158	62	24.83	95	132	23	1.0	86.11	
4	YASODHAI	52	F	148	53	24.20	91	128	21	0.9	61.18	
5	CHANDRAN	55	M	160	54	21.09	96	137	27	1.0	63.75	
6	DEIVASIGAMANI	57	M	157	56	22.71	85	129	22	0.9	71.73	
7	VENU	60	M	156	60	24.69	97	136	32	1.1	60.61	
8	ELLAPPAN	70	M	158	62	24.83	92	118	32	1.0	60.28	
9	RADHAKRISHNAN	70	M	165	64	23.52	97	121	26	1.0	62.22	
10	KANNIYAPPAN	65	M	158	61	24.43	94	126	25	1.0	63.54	
11	DHAYALAN	60	M	164	59	22.01	86	120	24	1.0	65.56	
12	JOTHI	60	F	165	60	22.05	63	113	36	0.9	62.96	
13	LOGU	50	F	168	58	20.54	90	121	24	0.9	68.47	
14	SEKHAR	80	M	165	57	20.95	78	112	35	0.8	59.38	
15	KANNAN	61	M	155	55	22.91	85	124	22	1.0	60.35	
16	RAJASEKHAR	70	M	163	60	22.64	92	135	31	0.8	72.92	
17	RAJAM	60	F	158	58	23.29	79	125	25	0.8	68.47	
18	PAPPAMMAL	65	F	158	55	22.08	87	110	28	0.8	60.87	
19	PAKKIRI	60	M	157	47	19.10	76	123	34	0.8	65.28	
20	RAJARAMAN	70	M	160	54	21.09	80	130	30	0.8	65.63	
21	CHINNAMMAL	35	F	158	60	24.09	97	133	26	1.0	74.38	
22	MEENAKSHI	45	F	162	59	22.51	94	122	33	0.9	73.52	
23	ANANDHAN	75	M	158	57	22.89	90	135	39	0.8	64.32	
24	ARUMUGAM	61	M	154	46	19.40	96	115	21	0.8	63.09	
25	ARUL	65	M	162	64	22.42	82	134	27	1.0	66.67	
26	MAHESH	70	M	163	62	23.39	75	108	24	1.0	60.28	
27	PATAMMAL	50	F	153	46	19.65	90	120	36	0.8	61.09	
28	ARJUN	80	M	165	61	22.42	84	105	21	0.8	63.54	
29	RAGUPATHI	53	M	158	62	24.89	96	111	38	1.2	62.43	
30	MINI	70	F	157	59	23.98	77	128	27	0.8	60.95	
31	MURUGAMMAL	50	F	153	48	20.50	76	132	22	0.8	63.75	
32	ARULANANDHAM	70	M	163	49	18.49	86	118	35	0.7	68.06	
33	ETTIYAPPAN	50	M	165	57	20.95	97	109	31	1.1	64.77	
34	MANI	80	M	160	58	22.65	92	124	24	0.8	60.42	
35	THILAGAM	60	F	158	57	22.89	84	134	34	0.8	67.29	
36	BABU	82	M	157	60	24.39	81	138	28	0.8	60.42	
37	ANBUMURUGARAJ	65	M	160	60	23.43	88	119	21	1.0	62.50	

38	JEGADEESAN	54	M	154	53	22.34	95	126	26	1.0	63.31	
39	ELAVARASI	70	F	155	58	24.16	91	133	31	0.7	68.47	
40	VALLI	65	F	152	51	22.07	80	116	35	0.8	56.44	
41	VINAYAGAM	60	M	157	54	21.90	76	109	22	0.8	75.00	
42	KANNAN	45	M	162	51	19.46	94	120	31	1.1	61.17	
43	SIVAKUMARAN	55	M	158	53	21.28	80	134	26	0.9	69.52	
44	JAMAL	70	M	165	58	22.65	90	117	23	0.9	62.65	
45	RAJESHWARI	60	F	157	60	24.39	76	126	34	0.9	62.96	
46	CHITHAMBARAM	60	M	165	57	20.95	84	106	38	1.0	63.33	
47	MOHAN	60	M	159	62	24.60	79	138	24	1.0	68.89	
48	GOWRI	68	F	162	57	21.75	91	117	27	0.8	60.56	
49	CHANDRAN	60	M	168	70	24.82	82	133	35	0.9	86.42	
50	AMMU	50	F	160	60	23.43	82	129	30	0.9	70.83	
51	MURUGAN	40	M	159	47	18.65	91	110	23	0.8	81.60	
52	GUNASEKARAN	55	M	168	70	24.82	78	121	28	1.0	82.64	
53	MUNUSAMY	48	M	164	62	23.13	93	135	31	0.9	88.02	
54	VASUDEVAN	55	M	160	56	21.87	83	106	24	1.1	60.10	
55	MADHAVAN	50	M	165	67	24.63	92	128	38	1.0	83.75	
56	HARI	48	M	156	58	23.86	85	119	23	1.0	74.11	
57	MANOHARAN	60	M	163	66	24.90	78	132	31	0.9	81.48	
58	SARANGAPANI	63	M	158	53	21.28	74	104	30	0.9	62.98	
59	PALANI	69	M	160	63	24.60	86	129	26	1.0	62.13	
60	PADMA	42	F	159	52	20.63	97	134	32	0.8	75.20	
61	IKBAL	76	M	170	70	24.42	90	103	23	1.0	62.22	
62	SELVAM	48	M	172	63	21.28	84	121	30	1.0	80.50	
63	DILIP	74	M	161	53	20.46	80	112	34	0.8	60.73	
64	ELAMARAN	62	M	172	63	21.28	74	117	37	1.0	68.25	
65	HEMACHANDRAN	61	M	158	52	20.88	91	138	24	0.9	63.40	
66	SUDHAKARAN	73	M	172	63	21.28	87	127	29	0.9	65.14	
67	CHINNAPPAN	77	M	164	58	21.64	78	104	22	0.8	63.44	
68	MURALINADHAN	60	M	166	52	18.90	86	131	30	0.9	64.20	
69	KRISHNAN	57	M	165	58	21.32	69	115	32	0.8	83.58	
70	PALANI	49	M	160	57	22.26	87	118	29	0.8	90.05	
71	FATHIMA BEGAM	67	F	151	53	23.24	84	127	22	0.8	57.09	
72	KUTTIAPPAN	60	M	163	65	24.52	95	106	28	1.0	72.22	
73	ANDAL	30	F	161	56	21.62	73	123	34	1.1	66.11	
74	AISHABEE	43	F	150	46	20.44	86	129	23	0.8	65.85	
75	VENKATASAMY	68	M	166	54	19.63	82	134	31	0.7	77.14	
76	SARASWATHY	59	F	159	62	24.60	70	122	28	0.9	65.88	
77	PRABAVATHY	55	F	162	64	24.42	92	116	36	1.0	64.22	
78	KANNIAPPAN	47	M	163	59	22.26	85	132	26	0.9	84.68	

79	SIVARAMAN	70	M	63	62	23.39	79	118	23	1.0	60.28	
80	PARTHIBAN	62	M	160	55	21.48	80	120	27	0.8	74.48	

STUDY GROUP											
S.NO	NAME	AGE	SEX	HEIGHT (cm)	WEIGHT (Kg)	BMI	FBS (mg/dl)	PP (mg/dl)	UREA (mg/dl)	CREATININE (mg/dl)	CREATININE CLEARANCE (ml/min)
1	DHAKSHANAMOORTHY	60	M	155	45	18.73	92	137	96	4.2	11.90
2	BALASUBRAMANI	32	M	152	40	17.31	88	112	148	5.8	10.34
3	CHINNAPPAN	40	M	160	60	23.43	86	138	126	8.8	09.46
4	NAGAMMAL	52	F	155	48	19.97	96	135	87	2.9	17.19
5	ERUSAN	55	M	160	49	19.54	87	102	121	5.4	10.71
6	VADIVEL	57	M	150	41	18.22	77	112	120	2.7	17.50
7	THAMBIRAN	60	M	148	38	17.34	98	132	94	3.1	13.62
8	MUTHU	70	M	157	42	19.43	85	124	172	3.5	11.66
9	KANNIYAPPAN	70	M	147	36	16.65	100	126	135	2.6	13.46
10	RAMAKRISHNAN	65	M	154	53	22.34	73	139	64	2.1	26.28
11	ARUMUGAM	60	M	160	62	24.21	85	127	67	2.1	32.80
12	BALAMMAL	60	F	157	43	17.44	98	120	72	3.0	13.53
13	VANATHAI	50	F	152	51	22.07	86	129	128	4.1	13.21
14	KANNAPPAN	80	M	153	48	20.50	83	113	54	2.2	18.18
15	BABU	61	M	157	54	21.90	93	128	155	7.2	08.22
16	YEHAPPAN	70	M	162	59	22.51	84	107	65	3.9	14.70
17	NAGAMMAL	60	F	156	58	23.86	98	124	108	3.1	18.88
18	MUNIYAMMAL	65	F	157	60	24.39	88	132	93	4.2	12.64
19	RAMDOSS	60	M	158	53	21.28	92	119	86	2.7	21.81
20	VAJRAVELU	70	M	158	57	22.89	99	137	64	3.2	17.31
21	CHELLAMMAL	35	F	156	56	23.04	68	103	174	6.4	10.84
22	SAKUNTHALA	45	F	156	41	16.87	98	138	98	3.2	14.36
23	KRISHNASAMY	75	M	165	57	20.95	95	129	60	2.4	21.44
24	ARUMUGAM	61	M	160	58	22.65	87	127	80	3.9	16.31
25	NARAYANASAMY	65	M	165	61	22.42	84	116	92	3.6	17.65
26	MUNUSAMY	70	M	159	62	24.60	73	132	162	7.4	08.14
27	LAKSHMI	50	F	162	57	21.75	85	111	97	4.5	13.45
28	RAJ	80	M	163	49	18.49	94	123	65	2.5	16.33
29	SELVARAJ	53	M	163	62	19.62	84	135	136	8.5	08.81
30	VALLIAMMAL	70	F	160	55	21.48	82	113	115	2.8	16.23
31	KANNIAMMAL	50	F	163	60	22.64	97	129	67	2.3	27.71
32	DHARMALINGAM	70	M	168	70	24.82	74	118	88	4.6	14.79
33	MAHENDRAN	50	M	168	62	18.43	93	124	191	7.9	09.81
34	RAMAN	80	M	160	56	21.87	92	129	67	2.8	16.66
35	CHINNAKOLANTHAI	60	F	152	56	24.24	87	112	64	2.5	21.15
36	RAGHAVAN	82	M	165	67	24.63	72	103	102	4.3	12.55
37	SUBRAMANI	65	M	163	66	24.90	92	129	185	9.9	06.94
38	SAMRAJ	54	M	168	64	22.69	98	134	116	7.5	10.19
39	NEELAMMAL	70	F	151	53	23.24	93	115	116	5.2	08.42

40	ANJALATCHI	65	F	155	55	22.91	87	132	60	2.8	17.39
41	DURAISAMY	60	M	163	62	23.39	83	121	68	3.3	20.87
42	MUNUSAMY	45	M	160	60	23.43	99	137	69	2.8	28.27
43	MANI	55	M	158	53	21.28	85	139	59	3.6	17.38
44	EGAMBARAM	70	M	160	63	24.60	78	128	103	9.7	06.31
45	ANJALAI	60	F	153	46	19.65	74	115	64	3.0	14.48
46	PERIYASAMY	60	M	160	63	24.60	80	132	60	2.2	31.81
47	VELLAYAN	60	M	170	70	24.42	94	131	112	7.8	09.97
48	MUNIYAMMAL	68	F	160	55	21.48	91	128	104	2.7	17.31
49	SUNDARAMURTHY	60	M	161	53	20.46	97	126	97	5.9	09.98
50	MURUGAMMAL	50	F	158	52	20.88	70	132	181	12.0	04.60
51	SHANKAR	40	M	172	63	21.28	93	134	32	2.6	30.28
52	ARUMUGAM	55	M	176	58	18.77	87	139	65	4.6	14.88
53	MUNUSAMY	48	M	164	58	21.64	80	137	138	7.7	09.62
54	MARUTHAN	55	M	158	52	20.88	91	134	87	2.1	29.23
55	PANCHACHARAM	50	M	164	61	22.76	92	126	123	5.4	14.12
56	MUNUSAMY	48	M	166	52	18.90	75	118	67	2.6	25.55
57	KANNIYAPPAN	60	M	157	47	19.10	84	128	74	2.6	20.08
58	MUNUSAMY	63	M	163	65	24.52	89	132	107	6.3	11.03
59	LAKSHMANA RAJA	69	M	158	50	20.08	98	138	88	9.0	05.47
60	RANI	42	F	150	46	20.44	68	112	163	9.6	05.54
61	RAJAMANI	76	M	157	44.5	18.08	89	109	69	6.4	06.18
62	PONROSE	48	M	162	64	24.42	79	115	192	12.7	06.43
63	SANTHANAM	74	M	157	50	20.32	88	117	104	7.3	06.27
64	SAMBUNATH	62	M	163	62	23.39	93	128	152	8.7	07.72
65	DHASARATHAN	61	M	160	48	18.75	88	132	134	15.9	03.31
66	ARUMUGAPILLAI	73	M	162	47	17.93	83	120	72	9.4	04.65
67	CHEZHIYAN	77	M	161	48	18.75	87	139	177	8.5	04.94
68	PAUL THANGARAJ	60	M	160	55	21.48	93	134	94	6.3	09.70
69	FRANKLIN	57	M	158	57	22.89	82	137	128	12.8	05.13
70	VENKATACHALAM	49	M	160	55	21.48	67	119	212	14.1	04.93
71	KAVANNA	67	F	160	44	17.18	65	101	87	8.0	04.73
72	SOLOMON	60	M	161	49	19.14	72	126	113	9.2	05.91
73	INDIRA DEVI	30	F	158	50	20.08	86	120	106	10.5	06.18
74	DHAMAYANDHI	43	F	166	54	19.63	88	123	121	10.0	06.18
75	ARUMUGAM	68	M	156	48	19.75	85	117	130	6.7	07.16
76	RATHINAMARY	59	F	162	61	23.82	89	109	158	12.7	04.59
77	POONGAVANAM	55	F	160	62	24.21	89	136	53	2.5	24.88
78	KUPPAN	47	M	157	40	16.26	85	120	92	4.3	12.01
79	SELVARAJ	70	M	165	60	22.05	94	114	205	2.3	25.36
80	THIRUVENGADAM	62	M	158	56	22.48	78	110	69	3.4	17.84